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# A SYSTEM OF MEDICINE



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SYSTEM OF MEDICINE

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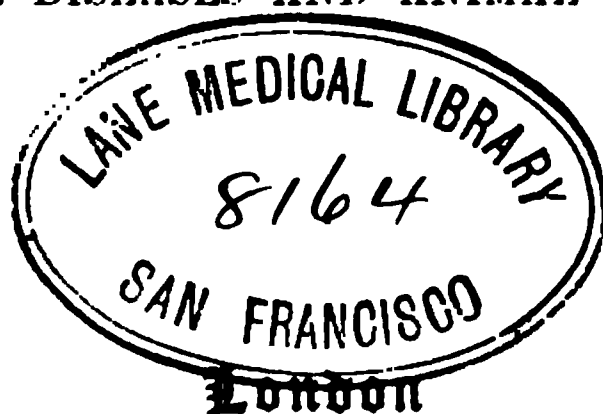
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VOLUME II

PART II

TROPICAL DISEASES AND ANIMAL PARASITES



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## PREFACE

THIS volume is entirely new in arrangement and largely so in substance. Some articles have been revised and removed from their position in the previous edition, mainly from the second volume, but the majority are new. By grouping all the Tropical Diseases and Animal Parasites together, this volume will, it is hoped, serve as a complete work on Tropical Medicine, and thus justify this alteration in the scheme of the *System of Medicine*. As many of the more important of the tropical diseases belong to the infections, and originally appeared in Volume II., it has seemed advisable to bring out the volume on Tropical Diseases at the same time as the new edition of Volume II., now Vol. II. Part I. After due consideration it has seemed most convenient to include all the animal parasites in this volume, and not to divide those of importance in tropical climates only from the others.

In order to provide an authoritative account of the animal parasites and carriers of tropical diseases, a knowledge of which is of the greatest importance to those engaged in the study and practice of Tropical Medicine, special articles by Zoologists have been included. These articles, or indeed condensed monographs, deal with the Protozoa (Prof. Minchin), Mosquitoes (Mr. F. V. Theobald), Blood-sucking and other Flies known or likely to be concerned in the spread of disease (Mr. E. E. Austen), and Ticks (Mr. R. I. Pocock), and have been freely illustrated so as to assist in identification of the animals described. Tropical Medicine is in its youth, and the advances incident to vigorous growth are so continuous and imminent that almost before an article is printed its conclusions may require

modification. This difficulty has been much in the mind of the contributors and Editors, and has rendered it unwise to attempt any formal or rigid classification of the diseases described. But since these advances whose economic is even greater than their scientific importance—for example, those in connexion with malaria—demand a working knowledge of the parasites and carriers of disease, it is hoped that the space given up to the descriptive zoological articles will be fully justified. The important article on Worms by Sir Patrick Manson has for this reason been brought thoroughly up to modern zoological knowledge and nomenclature by Mr. A. E. Shipley.

It would be tedious to enumerate the new articles and to detail the changes that have taken place in the articles on subjects dealt with in the first Edition of the *System*. For much advice and help most generously accorded, the Editors are deeply indebted to Sir Patrick Manson

T. C. A.

H. D. R.

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## INTRODUCTION

By Sir PATRICK MANSON, K.C.M.G., M.D., LL.D., F.R.S.

THE diseases affecting man have been classified in a number of ways, both scientific and practical. It cannot be claimed for the grouping of a certain number under the heading of "Tropical Diseases" that such an arrangement is in any sense a scientific classification. Nevertheless, it is a useful and practical one, and, moreover, is based on experience; on the circumstance that certain diseases are confined to tropical regions, or are especially prevalent in them, such limitation and prevalence being determined by peculiar etiological conditions which, in their turn, are determined or may be influenced by the meteorology of these regions.

The classification of disease on a climatic basis is supported by the additional circumstance that while some diseases are wholly or principally limited to the tropical belt, others—though only few in number, such as scarlet fever and rheumatic fever—are practically confined to cold or temperate climates. On the other hand the vast majority of diseases have no climatic limitations; syphilis, cancer, tuberculosis, and a hundred others are to be found in all climates and in nearly every country. Thus, then, arranging diseases from the standpoint of climate, we recognise three well-defined groups: a small group demanding the climatic conditions obtaining in cold or temperate climates, a larger group demanding tropical conditions, and a still larger group which appear to be entirely exempt from climatic restriction.

Looking at disease as a whole the question naturally arises why there should be these limitations in some instances and not in others, and why any disease should have climatic restrictions. How does temperature, for, broadly speaking, and especially in this instance, climate resolves itself ultimately into atmospheric temperature—how does temperature influence the distribution of disease? Climate influences the distribution of disease in one or other of several ways of which the following are the principal — (1) By the direct action of light, heat, moisture, and other meteorological conditions on the human body; (2) by the food special to different climates; (3) by the social arrangements and sanitary conditions more or less directly imposed by climate; (4) by the direct



or indirect bearing of atmospheric temperature on pathogenetic and associated organisms. Of these the last is in the case of tropical diseases by far the most important condition.

(1) Although many attempts have been made to trace and explain the effect of temperature on the physiological processes of the human body, more especially in reference to the pathological proclivities to which atmospheric heat and cold may conduce, it cannot be said that any important conclusions have been attained. With the exception of traumatism due to the sun (sunstroke), heat-syncope, erythema solare, and possibly lichen tropicus and heat-apoplexy (siriasis), there are no diseases that can be definitely attributed to the direct action of high atmospheric temperature on the human body. With the exception of frost-bite and in a measure but only in the case of individuals otherwise predisposed, chilblains and paroxysmal hæmoglobinuria, there are no diseases directly depending on the influence of cold on the human body. But, although we may not be able to indicate precisely the way in which our bodies are prejudicially affected by extremes of atmospheric temperature, especially prolonged high temperatures, our sensations, the loss of physical and mental energy, the modifications of physical characteristics undergone by white races when placed during several generations in tropical conditions, and the dark skins of all tropical races indicate that the white races on first arrival are not in all respects adapted for tropical conditions, that they are somehow prejudicially affected thereby, and that while living in tropical countries they are more open to certain pathological risks than are the natives of these countries.

(2) In a general way it may be affirmed that every considerable community has found its appropriate food and may be said, if this food be adequate in amount and of good quality, to thrive on it. But it sometimes happens that under stress of famine the staple foods are not obtainable, or if obtainable may be damaged. In such circumstances the people may be driven to eat substances containing toxic material. In this way lathyrism, ergotism, atropicism, manioc poisoning are acquired. Such diseases are practically limited to the areas in which such dietetic conditions occur, and some of these are necessarily tropical. Under the same heading might be placed the morbid conditions which arise from the inordinate use of certain intoxicants, such as Indian hemp.

(3) The social and sanitary conditions of most tropical countries, although they cannot be said to cause any special disease, are, nevertheless, as compared to the social and sanitary conditions obtaining in most temperate climates, eminently conducive to the prevalence of certain diseases such as leprosy, cholera, plague, dysentery. So much is this the case and so much more common relatively are these diseases in tropical countries that, practically, they have come to be regarded as tropical diseases. But they are tropical only in the sense indicated. They would thrive elsewhere were the social and sanitary conditions equally favourable. They are not essentially tropical.

(4) With rare exceptions—for the foregoing embrace but a small

proportion of what are regarded as tropical diseases—the limitations of certain diseases to warm climates are in no sense dependent on the action of temperature on the human body, or on food, or on social and sanitary conditions. Nor with few exceptions do they depend on the action of the atmospheric temperature on the disease-germ itself while the germ is located in the human body. They depend directly or indirectly on the requirements of the germ when it has escaped from the human body, and during its passage from human host to human host. During this passage the germs of tropical diseases demand tropical conditions; hence the geographical or rather climatic limitations of these diseases.

So far as we know them, the vast majority and all the important disease-germs of man belong to one or other of the following classes: *Bacteria*, *Fungi*, *Protozoa*, *Helminths*.

*Bacteria*.—Very few of the diseases special to the tropics or warm climates are bacterial, and it is difficult to explain how it is that these few even—Malta fever for example—should be so limited. For a bacterium is not injuriously affected by ordinary atmospheric conditions, and should be able to pass from man to man, whether directly, or indirectly from a saprophytic condition, in any climate. Accordingly the vast majority of the bacterial diseases of man are of wide distribution. On the other hand the vast majority of diseases having climatic limitations—tropical diseases among them—are caused by (a) *Fungi*, (b) *Protozoa*, (c) *Helminths*,—organisms which, as a rule, one way or another, require in their passage from host to host very special and often complicated conditions.

(a) *Fungi*.—Fungi living on the surface of the body are just as exposed to climate as are ordinary plants. Some of them demand a hot and moist climate, hence they are found only within the tropics and in particular parts of the tropics. *Tinea imbricata*, pinta, and probably other and as yet undetermined epiphytic diseases belong to this category. When we speak of a disease as being a tropical disease, we mean merely that the disease-germ can be acquired only in tropical conditions. Once the germ is acquired the disease runs its course in any climate. The only exception to this general statement lies in the epiphytic diseases. In those of them special to the tropics the germ itself, even after implantation and thorough establishment, still requires tropical conditions; on the patient quitting those conditions the germ dies and the disease it gave rise to disappears. In a sense, therefore, these epiphytic diseases are the only true tropical diseases.

(b) *Protozoa*.—The pathogenetic protozoa are responsible probably for a very large number of diseases. Many appear to be able to pass directly from host to host, unaffected apparently by the atmospheric conditions they encounter on the passage; that of small-pox and of most of the exanthematous fevers probably belong to this category. Others, on the contrary, demand special climatic conditions. Such are the germ of scarlet fever which does not spread in the tropics, and the germ of dengue which, conversely, does not spread in cold climates. That of the

first is killed or paralysed by heat ; that of the latter by cold. Or, it may be, they do not find appropriate transmitters except in special climatic conditions. Many of the protozoa under normal conditions acquire the power of successfully invading the human body only after certain developmental changes which take place after they leave their first host. Thus, according to Schaudinn, the germ of amœbic dysentery has to pass through a sporulating stage before it becomes infective, and this stage is accomplished only outside the body and in conditions of tropical heat. Hence amœbic dysentery is a tropical disease. Other protozoan disease-germs, notably those of malaria, yellow fever, trypanosomiasis and relapsing fever, require an animal intermediary to remove them from the body of their original host, foster them during a necessary stage of development, and reimplant them in the human host. These animal intermediaries being tropical, the diseases they disseminate are also necessarily tropical.

(c) *Helminths*.—The remarks on the diseases caused by protozoa apply equally to those produced by helminths, some of which can pass from host to host directly in any climate. These, of course, are more or less cosmopolitan : such are the common intestinal worms—*Ascaris*, *Trichocephalus*, and *Oxyuris*. Others again can pass directly from human host to human host, but demand a tropical temperature to secure the necessary preliminary development which enables them to live in the new host. Such is *Ankylostoma duodenale*, whose ova develop only under conditions of high temperature and adequate moisture. A third category requires an animal intermediary before it can establish itself in its definitive host. Thus, hydatid disease produced by the larva of *Tænia echinococcus* has to pass through the dog and man or sheep before its cycle is completed. Its hosts being cosmopolitan, the parasite is likewise cosmopolitan. But there are not a few of these helminths whose hosts or intermediaries, being limited by climatic conditions, give rise to diseases similarly limited. When the limitations are tropical, the diseases are tropical. Such are bilharziasis, filariasis, dracontiasis, distomiasis, and so forth.

These are the broad principles that determine the distribution of tropical diseases. They should be the guides in further investigation as well as in prevention. The peculiarities of tropical diseases are etiological rather than pathological. It is a recognition of this great truth that has contributed more than anything else to the expansion of our knowledge in recent years, and also to our ability to contend successfully with many tropical scourges against which we were formerly powerless.

An important matter, and one as yet hardly sufficiently recognised, is the disseminating influence that modern travel and means of communication are having on the spread of diseases formerly confined to perhaps very limited areas. We are familiar with the idea that trade routes and travel have spread bacterial diseases such as cholera, plague, and enteric fever, and directly infectious protozoan diseases, such as

small-pox. But as yet we have hardly grasped in a practical way the notion that the indirectly infectious protozoan diseases formerly held to be non-infectious may be and are being similarly disseminated. As a rule, but not invariably, these protozoan diseases in order to spread require more complicated conditions than the bacterial diseases. Nevertheless, now and again these complicated conditions have been supplied; for example, to introduce malaria successfully requires not only the introduction of the germ but also of the intermediary, an anopheline mosquito. This has probably occurred in many places, certainly in Mauritius, and probably will occur in the future in many other islands. The spread of yellow fever in a similar way is to be anticipated. The difficulties these parasites had to overcome in order to extend their boundaries is being rapidly removed by the rapidity of transit and the multiplication of opportunity supplied by modern methods of transport.

These are but two examples of a large group of diseases, with limitations at one time apparently fixed by nature, which in the future we have only too much reason to fear will be found throughout the greater part of the tropical world. It may be that, as in the case of yellow fever, expanding knowledge and expanding civilisation may do something to check this process; but the recent history of the extension of the area of sleeping sickness seems to indicate that knowledge sometimes comes when it is too late, or in circumstances in which it cannot be applied.

PATRICK MANSON.



## **ZOOLOGICAL ARTICLES**

**PROTOZOA**

**MOSQUITOES**

**BLOOD-SUCKING AND OTHER FLIES KNOWN OR LIKELY  
TO BE CONCERNED IN THE SPREAD OF DISEASE**

**TICKS**



## PROTOZOA

By PROF. E. A. MINCHIN, M.A.

THE name Protozoa was coined as an equivalent for the German Urthiere, meaning animals of a primitive or archaic type—a name given as far back as 1820 to the vast assemblage of microscopic animalcules which, from their appearance in infusions containing decaying animal and vegetable matter, were commonly termed Infusoria. To von Siebold belongs the merit, however, of giving a precise definition to the group, by pointing out that in the Protozoa the individual, whether living singly or combined with other individuals to form colonies, is in all cases a *single cell*. To put it in other words, in Protozoa the cell is an individual complete in itself, both physiologically and morphologically, in contrast with the higher division of the animal kingdom, the Metazoa, in which the body is always composed of many cells, differentiated amongst themselves for the performance of different functions, combined together to form a single complex individual, and incapable of maintaining a separate and independent existence. This is the sense in which the term Protozoa has always been used by zoologists; and von Siebold's generalisation, by giving a precise limitation to the group, brought about the exclusion from it, once and for all, of such forms as sponges and rotifers, which had often been referred to the Protozoa previously, but which henceforth ranked definitely as Metazoa.

The essentially unicellular nature of the Protozoa is a criterion by which it is easy to define them from a purely zoological point of view. It becomes, however, less easy to characterise them when we take into consideration the whole range of unicellular organisms, namely, the bacteria and the unicellular algæ and fungi, as well as those more distinctively animal in nature. And it may be said at once that in unicellular organisms it is not possible to maintain in systematic classification a hard and fast line between plants and animals. The difference between plant and animal is at first merely a difference of the mode of living, and cannot be used as a test of affinity, or for purposes of classification, until it has gone so far and been established so long that the cell has acquired indelible morphological characteristics resulting from the one or the other



mode of life. On this account it has been proposed by Haeckel to abolish the name Protozoa, as a division of the animal kingdom, and to include all unicellular organisms together under the name *Protista*, a category to rank as a distinct *kingdom* (Reich), equal in systematic value to the animal and vegetable kingdoms, between which the kingdom Protista would be a connecting link. Many modern authorities have adopted this method of meeting the difficulty, but the majority retain the Protozoa as a division of the animal kingdom, not only in deference to long-established usage, but because it represents a useful category and comprises forms having natural affinities with one another. If we try now to define this assemblage of forms from a wider point of view than that of the zoologist, we arrive at the following definition, or rather characterisation, of the Protozoa:—

Organisms in which the individual is unicellular—that is to say, is formed of a single undivided mass of protoplasm capable of independent existence in a suitable environment. The body always contains chromatin or nuclear substance, which may form a single mass, or may be divided into portions morphologically and physiologically differentiated from one another, or may be broken up into smaller masses, but which in all cases can be sharply distinguished from the general body-protoplasm or cytoplasm. The protoplasmic body may be naked at the surface, or covered by a cuticle or envelope which is not usually of the nature of cellulose. Organs serving for locomotion, and for the capture, ingestion, and digestion of solid food, are usually present, but may be entirely absent (holophytic, saprophytic, and parasitic forms). On the other hand, chlorophyl as a cell-constituent is absent, except in the holophytic Flagellata. Reproduction takes place by various modes of cell-division, which in the vast majority of cases is supplemented by some form of conjugation.

The above definition is of necessity somewhat vague, and does not sharply separate the Protozoa from primitive forms of plant-life, with which, as already explained, they are connected by gradual transitions. On the other hand, the characters given mark off the Protozoa from the bacteria, in which the body is limited by a definite capsule, and in which there is usually no obvious distinction of the protoplasm into nucleus and cytoplasm, the chromatin in these organisms being, according to recent researches, finely subdivided and scattered evenly throughout the protoplasm, so that the entire organism of a bacterium has rather the structure of a nucleus than of a complete cell.

The cytoplasm of Protozoa is commonly differentiated into a clearer and denser outer layer, the ectoplasm (ectosarc), and a more fluid, granular internal portion, the endoplasm (endosarc). The protoplasm contains various enclosures. First in importance is the *nucleus*, which is usually a compact, fairly conspicuous structure, and consists of chromatin combined in various ways with achromatic substance. Sometimes more than one such nucleus is present. In addition to the principal nucleus or nuclei, fine granules of extra-nuclear chromatin may sometimes be found scattered in the cytoplasm. Such granules are termed

*chromidia*. They may occur constantly in a given species, or may be formed from the principal nucleus at certain phases of the life-cycle; and sometimes the entire chromatin may be distributed in this manner, a principal nucleus being temporarily absent. When more than one nucleus is present, the nuclei may be strictly equivalent, or may be structurally and physiologically differentiated, in relation to processes either of functional activity or of reproduction.

Of frequent occurrence is a *contractile vacuole*, a clear drop of fluid which makes its appearance in the ectoplasm at some spot, grows more or less slowly to a certain size, then empties itself to the exterior by a rapid contraction, and is formed again. The contractile vacuole owes its origin to fluid draining from all parts of the body to a particular point, the fluid being water absorbed, probably, at the surface of the body from the surrounding medium. The water ejected from the contractile vacuole contains the soluble waste products of the metabolism of the protoplasm, and the function of the contractile vacuole must be looked upon as both respiratory and excretory. Contractile vacuoles are usually absent in those Protozoa which live as internal parasites of other animals. Forms which ingest solid food shew *food-vacuoles*, each a minute drop of water taken in with the prey.

Besides the enclosures already mentioned, the protoplasm contains, especially in the endoplasm, granules varying in size from minute to fairly large. Most of these are to be regarded as *metaplastic* in nature, *i.e.* as stages in the upward or downward metabolism of the material of the protoplasmic body.

Against unfavourable conditions such as desiccation or change of medium, many Protozoa are able to protect themselves by encystment—that is, the formation of a protecting envelope or *cyst* round the body. Under certain conditions the cyst is absorbed, or burst and thrown aside, and the contents set free.

Reproduction in Protozoa takes place generally by some form of *fission*. In this process a division of the nucleus is followed by that of the body as a whole. The fission may be *simple*, when first the nucleus, and then the rest of the body, divides into two parts; or *multiple*, when the nucleus divides either simultaneously, or by successive simple divisions, into a number of daughter-nuclei, following which the protoplasmic body breaks up into more or fewer daughter-individuals, each containing usually a single nucleus. The latter method is commonly termed *sporulation*, and the minute individuals produced may be termed generally *spores* (archispores). In this process the entire parent body is not necessarily used up in forming spores, but there may remain over a certain amount of residual protoplasm, which is destined to degenerate and die off.

Simple fission is known as *binary fission* when the two daughter-individuals are approximately equal in size. In other cases the division may be unequal, and sometimes to such an extent that the parent individual appears to bud off a single daughter-individual, rather than to

divide into two sister-individuals. In such cases the process is called *gemmation*.

The sporulation of Protozoa may lead to the formation of numerous active motile individuals, which are then spoken of as *swarm-spores*. A swarm-spore may be amœboid—that is to say, similar in character to a minute amœba,—and is then termed an *amœbula* (pseudopodiospore); or it may be flagellate—that is to say, be provided with one or more flagella as organs of locomotion,—and is then termed a *flagellula* (flagellospore). Like the larvæ of Metazoa, swarm-spores may differ very much from their parents in appearance and structure.

Growth and reproduction by fission may continue for many generations, but sooner or later, in most, if not in all Protozoa, a process of sexual union or conjugation is introduced into the life-cycle. The biological significance of this process is a matter of speculation, but in some cases at least it seems certain that the effect of conjugation is a rejuvenescence or renewal of the vital powers of an organism which has become effete and senile through long-continued vegetative activity. The sexual process may, however, intervene at different points in the life-cycle in different cases, and sometimes follows, sometimes precedes, rapid reproduction by fission. Conjugation is not necessarily combined, therefore, with reproduction, though it most frequently is so.

True conjugation (zygosis) among the Protozoa consists essentially in the fusion of nuclear substance from two different individuals (karyogamy). The individuals which go through this process are termed *gametes*; the nuclei which undergo fusion are known as *pronuclei*; the nucleus produced by their fusion is called a *synkaryon*; and if the fusion extends to the whole bodies of the two gametes the resulting individual is called a *zygote*. The gametes which conjugate may be adult individuals of the species (macrogamy), or may be very young individuals, the recent products of some form of multiplication (microgamy). They may, further, be similar and equal in all respects (isogamy), or may be differentiated in respect of size and structure (anisogamy). In the latter case one, the *microgamete*, regarded as male, is usually smaller, less laden with reserve food-material, and more active and motile; the other, the *macrogamete*, regarded as female, is more bulky, often very full of reserve material, and less or not at all motile. It is probably an invariable procedure for the nuclei of the gametes to go through processes of *maturation*, or preparation for conjugation, which always takes the form of elimination of a portion of the nuclear substance, some of the chromatin being either absorbed in the protoplasm or cast out from it as one or more “polar bodies.” The chromatin rejected in this way probably always includes the vegetative chromatin—that is to say, the chromatin which has regulated the processes of metabolism, such as nutrition, growth, cell-division, etc., in the non-sexual generations. In most cases, also, a portion of the generative or sexual chromatin is also eliminated. After the conjugation the chromatin of the synkaryon, at first purely generative, must be supposed to become differentiated in part into vegetative chromatin, which governs the

metabolism of the body through succeeding generations, until eliminated in preparation for the next act of conjugation.

In some cases not only are the conjugating individuals of the sexual generation, the so-called gametes, different from one another, but the individuals of the generation from which the gametes arise may be different from ordinary individuals of the species. The mother-cells of the gametes are then distinguished as *gametocytes*, and are usually of two kinds, microgametocytes and macrogametocytes. In highly differentiated forms the gametocytes and gametes form a series of generations distinguished as the "sexual cycle" from the generations of ordinary individuals forming the "vegetative cycle," and the two cycles form a regular alternation of generations. Thus a given species of Protozoa may be extremely polymorphic, and comprise a recurring cycle of dissimilar forms, which can be classed as of male, female, or indifferent character.

In some cases the two gametes which conjugate are observed to be sister-individuals derived by fission from the same parent gametocyte. In other cases the parent cell does not even divide, but its nucleus alone divides, and the daughter-nuclei give rise to, or become, the pronuclei which fuse to form the synkaryon. It is chiefly, though not solely, among parasitic forms that such processes of extreme in-breeding occur, to which the term *autoquamy* is applied. If any benefit be supposed to accrue to the organism from this process, it must result merely from the rearrangement or reconstitution of the nucleus.

In some cases among Protozoa it is observed that under certain conditions sexually differentiated individuals may, without going through any process of conjugation, proceed to reproduction of the ordinary type. To an event of this kind the term *parthenogenesis* is applied, a term employed in the first instance for the many known cases among Metazoa where an ovum, that is to say a germ-cell of definitely female character and produced by a female individual, develops without fertilisation. Parthenogenesis must not be confounded with non-sexual reproduction generally, of which it is merely a special case. In the Metazoa the male gamete or spermatozoön is so specialised and reduced in bulk that any development from it, except in union with the ovum, is quite impossible. In the less specialised male gametes of Protozoa, however, non-sexual development is possible, though very rare, and has been termed by Prowazek *etheogenesis*. Parthenogenesis and *etheogenesis* are initiated as a rule by changes which have the effect of setting the individual back, so to speak, from the male or female to the indifferent or non-sexual type, with subsequent reproduction on vegetative lines.

The Protozoa are divided into four classes—the Sarcodina, Mastigophora, Sporozoa, and Infusoria.

**Class I.—Sarcodina.**—Protozoa in which the body-protoplasm is naked, in which permanent organs of locomotion are absent in the adult, both locomotion and ingestion of food being effected by protoplasmic processes of temporary nature termed *pseudopodia*.

The typical body-form may be said to be a simple sphere, only realised

during the resting phase in *Amœba* and other forms which, like it, creep upon a solid substratum. In Sarcodina, however, which float freely suspended in the water, such as the Heliozoa and Radiolaria, the spherical body-form is retained in perfection, with pseudopodia radiating from it in all directions. On the other hand, the opposite extreme is seen in the semi-terrestrial Mycetozoa, forms which are adapted to live on damp tree-trunks, bark, fungi, etc. In these organisms the protoplasm forms large creeping masses, often measuring many centimetres in horizontal extent, but very thin in the vertical direction, termed *plasmodia*.

The greatest and most diagnostic difference in appearance between different Sarcodina is due to the differences in their pseudopodia, which vary from slender "filose" filaments (filopodia) to thick, coarse, "lobose" processes (lobopodia). The formation of pseudopodia may result in movement from place to place of the body as a whole, or the animal may remain stationary and send out its pseudopodia simply for the capture of food. As a rule, locomotion is most active when the pseudopodia are more lobose in type, less so when the pseudopodia are filamentous. The extreme of the lobose type is seen in those amœbæ in which the whole protoplasm flows forward steadily in one direction, so that the body when active is simply one large pseudopodium. The thicker and more lobose the pseudopodia, the less do they branch, but the more slender forms may branch repeatedly, and in the typical filamentous forms the branches anastomose into a delicate network, often spread over a considerable extent; such forms are termed "reticulose." All pseudopodia arise in the first instance from the ectoplasm, which is the seat of movement. When the pseudopodia are thick and lobose, a core of endoplasm flows into them, and they are consequently more fluid in consistence. Slender pseudopodia, on the other hand, are commonly composed of ectoplasm alone, and are more stiff and rigid.

The soft protoplasmic body of the Sarcodina may, in the free-living forms, be protected or supported by a secreted *skeleton*, primarily of an organic nature, but usually saturated and indurated by mineral salts, which in the vast majority of cases are either carbonate of lime or silica. The skeleton may be formed externally or internally to the body. In the former case it takes the shape of a shell, test, or house, into which the protoplasm can be retracted entirely or partially. Internal skeletons are laid down usually in the form of beams or bars of the skeletal material, which are commonly connected to form lattice-works more or less complicated in structure.

One nucleus at least is probably always present in any species of Sarcodina, as a more or less conspicuous body surrounded by a distinct membrane, and containing besides chromatin a considerable amount of achromatic substances, especially plastin, arranged in various ways. In addition to the nucleus there may be a greater or less quantity of extra-nuclear chromatin scattered in the cytoplasm in the form of fine granules or chromidia. Recent observations on the reproduction shew that the chromidia possess great importance, as reserve generative chromatin,



which comes into play when a fresh life-cycle is started by an act of conjugation; while the principal nucleus governs the "vegetative" activity of the body—that is to say, the nutrition, growth, and reproduction by ordinary division. In some forms phases may be found preparatory to conjugation in which the principal nucleus may be entirely absent and chromidia only are found in the cytoplasm. On the other hand, chromidia may be absent, the generative and vegetative chromatin being combined in the nucleus, from which is expelled the vegetative chromatin during the process of maturation prior to conjugation. The chromidia or generative chromatin can thus be compared as regards function to the micronucleus of the Infusoria (see p. 114), and the principal nucleus or vegetative chromatin to the macronucleus.

The cases in which species of Sarcodina have been described as lacking a nucleus altogether (Haeckel's so-called Monera) are probably to be explained either by defective technique and observation or by the nucleus being represented temporarily in the form of chromidia. With increase of body-size the number of nuclei present may also undergo increase by growth and division, often to many thousands. In such cases the nuclei of a given individual are similar and equivalent to one another, and not differentiated in structure or function.

A contractile vacuole is commonly found, but appears to be quite absent in some groups (Mycetozoa, Radiolaria, most Foraminifera); in other cases more than one may be present. Food-vacuoles are usually formed when solid food is ingested. The metaplastic enclosures of the protoplasm may include crystals and other bodies too varied in nature to be enumerated in a general account.

All Sarcodina exhibit resting phases, during which they either shelter against unfavourable conditions, or enter upon a period of reproductive activity. Encystment is a common phenomenon in these circumstances. In Sarcodina which have a shell or test the protoplasm is withdrawn into it during the resting phases. A cyst may be formed within the shell by the protoplasm; when the animal enters again upon the active phase, the cyst is absorbed and the shell reoccupied.

Reproduction in the Sarcodina takes one of two forms—(1) simple fission in some form during the active condition of the animal; (2) sporulation in the resting state. The latter is commonly found associated with some method of conjugation.

(1) Multiplication by simple fission appears to be in abeyance only in some of the larger marine Sarcodina, such as Radiolaria and Foraminifera, forms for the most part with a more or less complicated shell or skeleton or body-structure. With these exceptions the rule in the group is reproduction by fission. Colony-formation, through incomplete separation of individuals produced by fission, as frequently seen in other classes of Protozoa, does not appear to be common in Sarcodina.

(2) Sporulation is probably of very general occurrence in this group, though in many forms it has not yet been described. It usually takes place within a cyst, though not always, and results in the breaking-up of

the nucleus and cytoplasm, to form numerous small uninucleate individuals which are set free as *swarm-spores*, either amœbulæ or flagellulæ. The flagellulæ represent always a temporary phase, and later lose their flagella, with or without conjugation having taken place, becoming amœbulæ, which in their turn develop into the adult organism.

In Sarcodina the sexual process exhibits great variety, both in its methods and in its relations to the life-cycle as a whole. Conjugation (zygosis) where it has been observed takes place most frequently between swarm-spores, especially flagellulæ, two of which become completely fused, both in nucleus and cytoplasm, to form a uninucleate zygote. In many cases the gametes, whether amœbulæ or flagellulæ, may be differentiated in size and structure into male and female elements (*anisospores*). In other cases again a third or indifferent form of swarm-spore (*isospore*) may be formed which develops directly into the adult without conjugation. The extreme of complication is reached where, as in some Lobosa and many Foraminifera, true alternation of generations is observed. The adult individuals are then of two kinds: one form, termed by Schaudinn a *schizont*, giving rise only to isospores, which develop without conjugation; the other, termed a *sporont*, giving rise to anisospores which conjugate; and the zygotes develop into schizonts. In some cases the conjugation is not between swarm-spores, but between adults (macrogamy). True conjugation, with nuclear fusion or karyogamy, must be carefully distinguished from a process of not uncommon occurrence termed *plastogamy*, in which the protoplasm of two or more individuals undergoes amalgamation, the nuclei remaining separate.

The Sarcodina may be divided conveniently into five subclasses, some of which, however, do not include parasitic forms of interest to medicine, so far as present knowledge extends.

Subclass I.—*Amœbæa*.—Amœba-like forms, with or without a shell, but usually without internal skeleton; usually of creeping habit, occasionally floating. Pseudopodia of various types.

The classification of the Amœbæa is extremely difficult, as no sharp characters are to be found by which they can be grouped, and the most extreme types are connected by transitions. Obvious morphological characters are the nature of the pseudopodia and the presence or absence of a shell. In the lack, however, of more extended knowledge of the life-histories of these organisms, present classifications must be regarded merely as provisional methods of conveniently grouping them, and not in any way as indicating their natural affinities. Hence we find that no two authors are in agreement in their modes of classifying the forms comprised in this order. For the purposes of the present article it is sufficient to divide the Amœbæa into Reticulosa, with filamentous, usually reticulate pseudopodia, and Lobosa, with lobose pseudopodia. The Lobosa may then be further subdivided into Nuda (*Gymnamœbæ*), with naked protoplasm, and Testacea (*Thecamœbæ*), provided with a shell.

1. The Reticulosa, sometimes classified as a special subclass under the name *Proteomyxa*, comprise the naked amœboid forms characterised

by slender, filamentous, usually net-like pseudopodia. The Reticulosa do not include any forms of special interest to medicine, as parasites of man or other animals. One of them, however, belonging to the family *Zoosporida*, namely the well-known parasite of cabbage plants, *Plasmodiophora brassicae* Woronin, deserves mention, as it has figured a good deal in recent cancer researches, and its intracellular stages in the roots of the cabbage have been compared with the well-known "Plimmer's bodies" in cancer. *Plasmodiophora* attacks any species of the genus *Brassica*, as well as allied genera of *Crucifera*, and produces pathological growths on the roots in the form of knotty swellings. The cycle begins with spores from which small flagellulae are set free, each with a single flagellum. The minute flagellulae find sufficient moisture to swim in damp earth and attack and penetrate the roots, becoming small amœbulæ which pass into the cells of the parenchyma, where they are found in the cell-sap, several in each cell. The host-cells multiply, and become later hypertrophied and of abnormally large size. The amœbulæ in each cell fuse together to form plasmodia, and their nuclei multiply. After a certain number of vegetative divisions, the nuclei of the plasmodium enter upon the generative phase by breaking up into chromidia, which are partly absorbed, partly reconcentrated to form small generative nuclei. These divide by karyokinesis twice, and then the protoplasm becomes segmented round the nuclei to form small uninuclear corpuscles, the gametes, which fuse in pairs in an autogamous manner. The zygotes become surrounded by a tough wall to form the very numerous minute round spores, which are set free by decay of the plant-tissue, and under suitable conditions liberate the minute flagellulae which initiate a fresh infection and a new vegetative cycle. By some authorities this parasite is included amongst the Mycetozoa (see p. 21), on account of the formation of plasmodia.

2. The Lobosa Nuda comprise the various genera of Amœbæ, such as *Amœba*, and allied genera. The majority of them are free-living forms, but parasitic amœbæ are found in various animals. A species very easily obtained is *Amœba blattæ* Bütschli, found almost invariably in the proctodæum of the common cockroach (*Blatta orientalis*).

At least three species of *Amœba* are internal parasites of the human body,<sup>1</sup> and have been given the generic name *Entamœba*; a genus to be defined, however, only by a parasitic habit of life, and not by structural characteristics, unless the absence of a contractile vacuole is to be considered a diagnostic feature. Two of the species in question appear to be perfectly harmless to their hosts, and are perhaps to be regarded as commensals rather than parasites: these are *Amœba coli* Lösch, occurring chiefly in the anterior part of the large intestine, and *A. buccalis* Prowazek, from the mouth of persons suffering from dental caries. The third human species of *Amœba* is pathogenetic in its action, and has been named by Schaudinn (74) *Entamœba histolytica*; it is regarded as the cause of tropical dysentery. (See article "Amœbic Dysentery.")

<sup>1</sup> Many more species of doubtful validity have been described and named. See Doëlein (22) and Braun (8).



It occurs not only in all parts of the intestine, but may also penetrate the liver, stomach, kidneys, etc., causing abscesses in these organs. *Amœba histolytica* has commonly been confused with *Amœba coli*; but according to Schaudinn they not only differ totally in their life-cycles, but they are distinguishable by the following characters (compare also Verdun, 93). In *Amœba coli* (Fig. 1) the ectoplasm is not visible as a distinct layer, except during the formation of a pseudopodium, when it appears as a hyaline projection of the surface, into which the granular endoplasm flows; in consequence the pseudopodia are soft and fluid. Its nucleus is large, sub-central in position, and, being rich in chromatin, stains deeply in preparations. In *Amœba histolytica* (Fig. 2), on the other hand, the ectoplasm forms a distinct superficial layer, and the pseudopodia not only grow out from it, but are formed entirely by the hyaline substance of the ectoplasmic layer; hence the pseudopodia of this form are more tough and rigid in consistence. The nucleus is small and very poor in chromatin, hence staining with difficulty, and in position it is excentric or even superficial, appearing sometimes as if flattened out against the ectoplasm. Finally, in *Amœba buccalis*, according to Prowazek (65), the characters of the protoplasm resemble those of *A. histolytica* in the presence of a distinct ectoplasm, of which also the pseudopodia are entirely composed, but the nucleus is large and more or less central in position, as in *A. coli*, though at the same time poor in chromatin. Schaudinn considers that the properties of the two intestinal amœbæ are correlated with the peculiarities of their protoplasm. *Amœba coli*, with its soft, semi-fluid pseudopodia, is unable to force its way into the epithelial cells of the gut, and nourishes itself on bacteria and various substances contained in the intestines. *A. histolytica*, on the other hand, with its tougher pseudopodia, is able to attack the epithelial cells and to penetrate into the submucous tissues, where it causes ulcers, nourishing itself on tissue-elements, blood-corpuscles, etc. *Amœba buccalis* feeds chiefly on leucocytes, bacteria, etc., in carious teeth.

The life-cycles of *Amœba coli* and *A. histolytica* have recently been studied by Schaudinn (74). The development is very different in the two cases.

*Amœba coli* (Fig. 1) multiplies in the large intestine by binary fission of the ordinary kind, and also by a rapid process of multiple fission (Fig. 1, G) to form eight small amœbæ which wander off, feed, and grow. In this way is explained the great disparity of size, varying between eight and 50  $\mu$  in diameter, observed between different amœbæ of this species. The "vegetative" reproduction by these two kinds of fission goes on for a variable time, lasting longer when the fæces are more fluid, but soon coming to an end when the fæces become hard. Then the amœba becomes encysted and passes out of the gut. The cyst is at first only a delicate gelatinous envelope, within which the sexual cycle begins its course. Each cyst contains a single uninucleate amœba, the nucleus of which divides into two, each daughter-nucleus going to opposite poles of the cyst, and then the protoplasm becomes partially divided into two

masses centred round each of the nuclei. Each nucleus now becomes partially or entirely resolved into chromidia, some of which, together with the remains, if any, of the original nucleus, are absorbed or cast out. From the remaining chromidia of each mass of protoplasm a new nucleus is formed, and the reconstituted nuclei, which may be regarded as com-

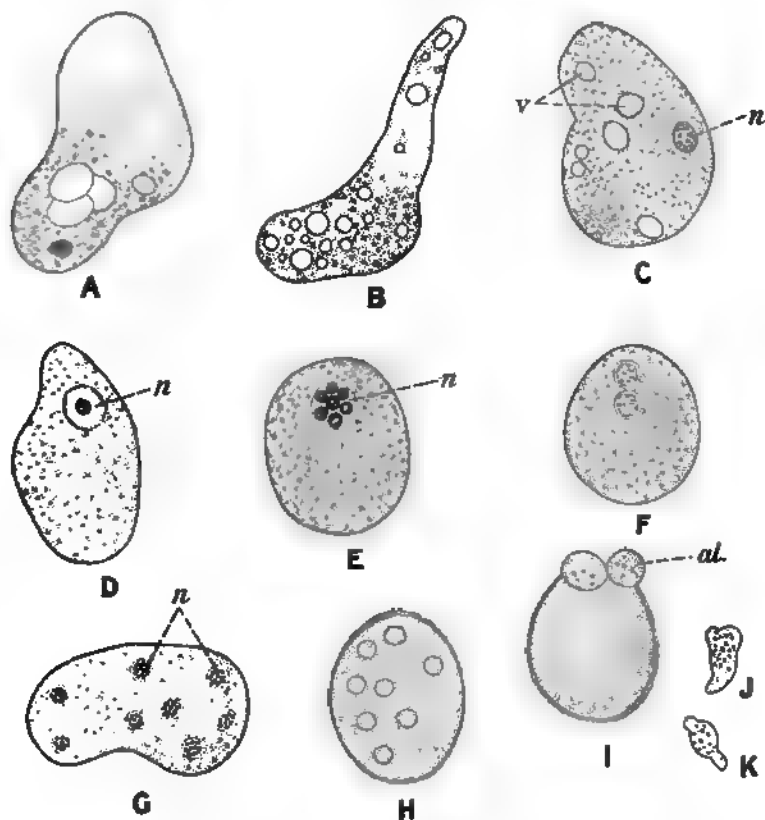


FIG. 1.—*Amoeba coli*. A and B, living amoebae, shewing changes of form and vacuolation in the protoplasm; C, D, E, amoebae shewing different conditions of the nucleus (n); F, a specimen with two nuclei, preparing for fission; G, a specimen with eight nuclei preparing for multiple fission; H, an encysted amoeba containing eight nuclei; I, a cyst from which young amoebae (al) are escaping; J, K, young amoebae free. After Casagrandi and Barbagallo.

posed of generative chromatin, proceed to undergo further reduction. Each divides into two, and one half of each is absorbed or cast out as a polar body: the remaining nucleus divides again, and again one half is rejected. When this process of maturation is completed the delicate gelatinous envelope becomes reinforced by the secretion internal to it of a thick cyst-wall, and the contained protoplasm shrinks to some extent, the two partially distinct portions fusing into a single mass, in which are

seen the two matured generative nuclei. Each of these nuclei now divides into a pair of daughter-nuclei, which may be distinguished from one another as the active and passive pronuclei. The active pronucleus of each pair moves across the body and fuses with the passive pronucleus of the other pair, so that now the cyst contains two zygote-nuclei or synkarya. Each synkaryon divides into four, so that the entire cyst contains eight nuclei. At this stage the cyst requires to be swallowed by a fresh host. If that occur, the contents escape in the large intestine of the host, and the protoplasm divides up round the eight nuclei to form eight small amœbæ (Fig. 1, H), which, just as in schizogony, start on the vegetative phase and thus complete the life-cycle.

*Amœba histolytica* (Fig. 2) multiplies in the active condition both by

binary fission and by a process of irregular gemmation. In the latter case multiple nuclear division leads to the formation of small individuals constricted off from the surface of the parent animal, the number thus formed being indefinite, in contrast to the definite number of eight formed by schizogony in *Amœba coli*. The average size of a full-grown individual varies between 25 and 30  $\mu$  in diameter, with a nucleus of 4-6  $\mu$  in diameter. When the conditions are unfavourable for continued vegetative activity, as for instance when the process of healing commences in the host, the formation begins of resistant phases, not however, of cysts in this case, but of spores. The nucleus first gives off chromidia into the protoplasm, after which the remains of the nucleus are rejected. The chromidia collect near the surface of the body, and

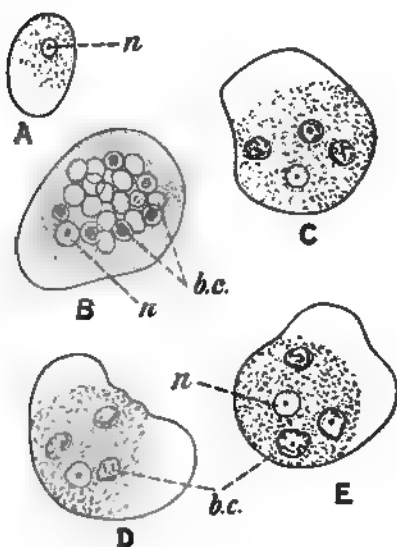


FIG. 2.—*Amœba histolytica* Schaud. A, young specimen; B, an older specimen crammed with ingested blood-corpuscles. C, D, E, three figures of a living amœba, which contains a nucleus and three blood-corpuscles, to show the changes of form and the ectoplasmic pseudopodia; n, nucleus; b.c., blood-corpuscles. After Jurgens.

the ectoplasm grows out into little elevations, each containing numerous chromidia, which undergo separation from the parent body as small spheres of protoplasm, destined to become the spores. The remainder of the amœba degenerates. The spores become surrounded by a tough yellowish-brown envelope, which prevents further study of the nuclear substance contained in them. It has been shewn experimentally that dysentery can be produced in cats fed with material containing dried spores, great numbers of amœbæ making their appearance in the intestine

and faeces. Only the spores, however, can communicate the infection in feeding experiments. The details of the development of the spores are not known; possibly they may set free some form of swarm-spore which represents the gamete-phase and goes through a process of conjugation in the new host, but nothing is known of conjugation in the life-cycle.

In *Amoeba buccalis* Prowazek has observed multiplication by binary fission, and also a break-up of the nucleus into chromidia, followed by an apparent resolution of the protoplasmic body into small spherical bodies, perhaps a process of spore-formation as in *A. histolytica*.

Before leaving the subject of the human parasitic amœbæ, mention must be made of the peculiar bodies found in the ascitic fluid which Schaudinn regards as independent amœboid organisms and has named *Leptenia gemmipara*. The nature of these bodies must be considered very doubtful for the present. For fuller information with regard to them see Doflein (22) and Braun (8).

The peculiar organism which Castellani has described from the human intestine under the name *Entamoeba undulans* is certainly in no way related to the forms dealt with in the foregoing paragraphs. It is described as having an oval body with an undulating membrane, and as protruding from time to time a single long narrow pseudopodium, sometimes from one part of the body, sometimes from another. It is probably a phase, normal or abnormal, of some species of intestinal flagellate.

3. The Lobosa Testacea (*Arcellina* Bütschli) comprise a number of genera, mostly of fresh-water habitat, characterised by the possession of a shell with a large aperture, through which the protoplasm sends out lobose pseudopodia. None of them are known as parasites.

Subclass II.—*Foraminifera*.—The forms comprised in this order are characterised by filamentous, usually very reticulate pseudopodia, and by the possession of a shell or test, most variable as regards material, but more usually calcareous, and shewing also the greatest possible variety in form, but always possessing at one pole a large aperture through which the protoplasm streams out or is retracted into the shell. They are mainly of marine habitat, very beautiful and interesting in themselves, but having no special claim to consideration on the part of the medical man. One order, however, the Gromiidea, deserves mention here for two reasons. First, the forms comprised in this order, mostly of fresh-water habitat, approach very closely to some of the Testacea and shew that the line of demarcation between Amœbæa and Foraminifera is a very artificial one. Thus *Euglypha* (Foraminifer) and *Diffugia* (testaceous amœba) scarcely differ in any important point of structure, except that the former has filamentous, the latter lobose pseudopodia. Secondly, one member of this family, though not exactly a human parasite, comes into relations with man; this is *Chlamydomorphys stercorea* Cienkowsky (*Platium stercoreum*), found in the faeces of man, various mammals, and other vertebrates (Fig. 3). The reproduction of *Chlamydomorphys stercorea* has been investigated by Schaudinn (74).

Subclass III.—*Mycetozou* seu *Myxomycetes*.—The forms comprised in

this order may be regarded as Sarcodina adapted to a semi-terrestrial life, living in moist places such as damp bark, decaying animal or vegetable matter, dung. In consequence they have many peculiar features, including a process of multiplication by spores, which led to their being classed formerly as fungi.

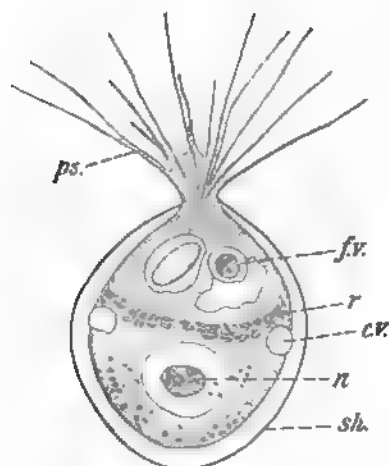


FIG. 3.—*Chilomastix stercorea*. *ps.*, pseudopodia; *f.v.*, food vacuoles; *e.*, equatorial zone of granules; *c.v.*, contractile vacuole; *n.*, nucleus; *sh.*, shell. The chromidia surrounding the nucleus are not shown. After Cienkowski.

Subclasses IV. and V.—*The Heliozoa and Radiolaria*.—The Sarcodina comprised in these two groups are typically floating forms, of marine or fresh-water habitat, in which the body is of spherical form, and sends out slender radiating pseudopodia, which are usually stiff and do not branch. An internal spicular skeleton may be present or absent. Since the members of these subclasses are not known as parasites, and are not, it may be added, at all likely to be found living under such conditions, the reader desirous of further information about them is referred to the larger treatises.

**Class II.—Mastigophora.**—Protozoa in which one or more permanent organs serving for locomotion or for capture of food are present in the adult in the form of flagella.

A typical individual of the class Mastigophora is of small size, often excessively minute, rarely visible to the naked eye, and never equalling the relatively gigantic proportions attained by many Sarcodina. There is, however, a pronounced tendency to colony-formation in this class, and the colonies may reach a considerable size. Whether as separate individuals or as colonies, the Mastigophora may be either free-moving or of sessile habit, being in the latter case attached to some object by a portion of the body, which may be drawn out into a stalk or peduncle.

From the biological point of view the Mastigophora are interesting, because every known mode of nutrition occurs amongst them. Many species are even capable of more than one form of metabolism, according to the circumstances of their environment, so that we find species which may be holophytic in some circumstances and holozoic or saprophytic in others. In most cases, however, a given species is irrevocably committed to either the holozoic, saprophytic, or parasitic mode of life.

The body shews variations of form and habit depending on differences in structure. In a few cases the protoplasm is quite naked at the surface, as in the Sarcodina, and the body is amoeboid, with a more or less distinct division of its substance into ectoplasm and endoplasm. In the great

majority of cases, however, the surface of the body is either limited by a cuticle or *periplast*, representing a differentiation of the most superficial layer of the protoplasm, or is enclosed in a more or less rigid secreted membrane or envelope; in both cases a differentiation of the body into ectoplasm and endoplasm is absent. The periplast may be extremely thin, permitting changes in body-form which are due to contractility, and manifest themselves in so-called euglenoid movements, *i.e.* ring-like contractions or swellings of the body passing along from one extremity to the other in a peristaltic manner. Such forms are termed *metabolic*. In most cases, however, the body has a definite contour, which may be combined with great flexibility, or with more or less complete rigidity of form. When a secreted envelope is present, it may take the form of a test or house standing off from the body, or of a cell-membrane in contact with the superficial protoplasm. The holozoic Mastigophora, which absorb solid food-particles, may do so at any point of the body-surface, or at a particular region or spot, which then may be marked by a definite and constant aperture or cell-mouth (cytostome). The cell-mouth leads usually into a short tube or *oesophagus* which ends blindly in the body protoplasm. In holophytic, saprophytic, and parasitic forms, nourishment is absorbed by diffusion through the superficial layer of the body, and a mouth-apparatus is either entirely absent, or is retained in some of the free-living species as an excurrent duct and aperture for the contractile vacuoles.

Great external differences in appearance between different Mastigophora are produced by the manifold variations in the number, form, and arrangement of the flagella. Commencing with the simplest case, in which but a single flagellum is present, it is usually situated at the extremity of the body which is anterior in movement, and acts as a *tractellum*; that is to say, it performs peculiar lashing movements by which the body, if free-swimming, is dragged after it, generally in a more or less jerky manner. In fixed forms the result of these movements is to cause a current of water towards the base of the flagellum, so that solid particles suspended in the water are made to impinge upon the body in this region. In a few cases, however, the flagellum is said to act as a *pulsellum*—that is to say, to be situated at the pole of the body which is posterior in movement and to propel the body forward, like the tail of a spermatozoön. The condition with a single flagellum is termed *monomastigote*. There may, however, be two flagella (*oligomastigote*) or more than two (*polymastigote*). When there are two or more flagella, they may be arranged in various ways, of which the following are some of the more important types:—In (1) the *paramastigote* condition a small accessory flagellum is inserted by the side of a larger, forwardly directed, principal flagellum. In (2) the *heteromastigote* condition (Fig. 4), one or more<sup>1</sup> flagella project forwards from the anterior termination of the body, and another

<sup>1</sup> The term *heteromastigote* is generally restricted to the condition in which only two flagella are present, but is equally applicable to the forms, such as *Trichomastix* and *Trichomonas*, in which more than two flagella occur.

flagellum arises at or near the origin of the forwardly directed flagella, but is directed backwards, running close along the body-surface to the posterior end, and there projecting freely beyond the body to a greater or less extent, being as a rule longer than the anterior flagella. In this arrangement the anterior flagella have the usual whip-like movements and act as tractella ("Peitschengeissel," lashing flagella). On the other hand, the backwardly directed flagellum performs undulating, wave-like movements, and appears to be an organ more for a creeping than for a swimming mode of locomotion; it is placed on the side of the body in contact with some solid surface, and by its movements causes the body to glide along ("Schleppgeissel," trailing flagellum). In (3) the *isomastigote* condition there are two flagella, arising together at the anterior pole, which are equal in size and similar in orientation. In (4) the *holomastigote* condition there are numerous flagella scattered evenly over the body, a condition only known, however, in one genus.

In addition to a flagellum, the body may bear on the exterior a structure termed an *undulating membrane*, as in the well-known genus *Trypanosoma* (Fig. 6), that is to say, a protoplasmic membrane running along the body like a fin, which by its contractility can perform undulating movements like those of a sail flapping in the wind, or, better still, like the waves of movement that can be seen in the tail-fin of an eel or the dorsal fin of a pipe-fish (*Syngnathus*). Undulating membranes are found chiefly, if not exclusively, in parasitic forms, and are perhaps to be regarded as organs adapted for locomotion in a medium containing many solid bodies or particles in suspension, as in the blood or the contents of the intestine. The origin of the undulating membrane is probably to be sought in the heteromastigote condition above described, as a web or keel of contractile protoplasm uniting a primitively free, gliding flagellum to the surface of the body. There are many parallel cases which indicate such an origin. Thus, in the genus *Trichomastix* the body has three anterior flagella and a posteriorly directed gliding flagellum. In the closely allied genus *Trichomonas* (Figs. 29, 30) the arrangement of the flagella is similar, but the gliding flagellum forms the free edge of an undulating membrane, just as does the single flagellum of *Trypanosoma*. The relation of undulating membranes to flagella is an important point in considering the affinities of forms possessing these structures, and will be discussed further in describing the structure of *Trypanosoma* (p. 29). The peculiar forms grouped in the order Choanoflagellata are remarkable for the possession of a structure termed a collar, a protoplasmic membrane which forms a hollow tube enclosing the basal portion of the flagellum.

The protoplasmic body of the Mastigophora invariably contains a distinct nucleus, and commonly also other structures of various kinds, which will be dealt with first. Food-vacuoles are found in holozoic forms. They may arise at any point of the body, but where there is a definite mouth-apparatus they are formed at the base of the oesophagus. Contractile vacuoles are commonly found, but are totally absent in some parasitic forms, such as *Trypanosoma*. In its highest elaboration, seen



in such a form as *Euglena*, the vacuole-system consists of a number of small contractile vacuoles which empty themselves into a single large vacuole or reservoir, which in its turn evacuates its contents into the oesophagus.

A number of cell-organs are to be seen in holophytic forms, which can only be mentioned very briefly here, as they are not found in any known parasitic forms. Such are (1) *chromatophores*, bodies impregnated with a pigment, usually green and of the nature of chlorophyl, the means by which the organism carries on its plant-like nutrition; (2) *pyrenoids*, refringent bodies in the chromatophores, usually covered by a sheath of amyloid substance formed by the constructive holophytic metabolism; (3) *paramylum-bodies*, masses of a substance allied to starch; and (4) *stigmata*, minute bodies impregnated with a red pigment, hæmatochrome, a single stigma being usually found attached to the oesophagus near the base of the flagellum. It is probable that the stigma is the seat of the sensitiveness to light that is so marked a feature of many flagellates. In some forms the whole body is coloured red by hæmatochrome pigment contained in minute oily particles scattered over the whole surface of the body. Such red-bodied species are sometimes so abundant as to impart a red colour to the water in which they live.

In addition to the cell-organs already enumerated, the protoplasm may contain various granules and enclosures, probably of metaplastic nature.

The nuclear apparatus of the Mastigophora is always in relation with the locomotor apparatus. In the simplest cases the flagellum or flagella arise direct from the nucleus itself, as in *Trichomonas* (Fig. 29). In other cases the flagellum arises from an intermediate body or zygoplast (Prowazek) which is connected with the principal nucleus by a filament. But in many, perhaps in most, cases the flagellum arises independently of the principal or trophic nucleus from a small, usually minute, kinetic nucleus, the blepharoplast. This subdivision of the nucleus in Mastigophora into trophic and kinetic portions must on no account be confused with the subdivision into micronucleus and macronucleus seen in the Infusoria, since in the latter the micronucleus represents generative or sexual chromatin, the macronucleus vegetative chromatin. Apart from the above-mentioned subdivision of the nuclear apparatus, the Mastigophora are never multinucleate—that is to say, there is never more than one principal nucleus, except, of course, when the preparations for reproduction are commencing. The principal nucleus varies in structure, but most usually contains a distinct nuclear corpuscle or karyosome. Chromidia are generally absent, but a single large chromidium has been observed by Prowazek in the gamete-producing forms of *Bodo lacerta*. The blepharoplast appears usually homogeneous, but in some cases is described as having differentiated central and peripheral portions. Where there are more flagella than one, their blepharoplasts may be fused into a rod-like structure.

The reproduction of the Mastigophora, considered generally, is on the



same lines as that of the Sarcodina—that is to say, multiplication by fission in the free, active condition, and sporulation in the resting stage, usually within a cyst, are both found, the latter method generally connected with conjugation. Multiplication by fission is invariably of the simple binary type, and almost always longitudinal to the principal axis of the body. The division commences with that of nucleus and blepharoplast, and following the latter the flagellum, if single, either becomes divided also, or a new flagellum is formed by the side of the old one. Other cell-organs, if present, may either undergo reduplication by fission or become re-formed in one of the two daughter-individuals. The nucleus may divide directly or by a simple form of karyokinesis in which the karyosome plays a part analogous to that of the centrosome in Metazoa.

Sporulation during the resting state is of frequent occurrence, especially in the larger, more specialised forms, such as the marine *Noctiluca* or the common fresh-water *Euglena*. The swarm-spores liberated are always flagellular, which may, however, differ markedly from the parent-form. An amoebula stage, if it occurs at all, is extremely rare. As in the Sarcodina, the swarm-spores may be non-sexual isospores or sexual anisospores.

The details of conjugation, and the preparations for it, are very inadequately known in this group, and it is very difficult at present to make generalisations, but so far as our knowledge extends the types of conjugation are as follows. The most primitive method is union, ending in complete fusion of nucleus and cytoplasm, between two individuals not differing either from one another or from the ordinary individuals of the species, except in so far as their nuclei may have undergone processes of maturation by elimination of nuclear substance. This method is found amongst the simpler, more minute forms, and is frequently accompanied by formation of a cyst round the two conjugating individuals, and subsequent rapid multiplication of the zygote to form numerous small individuals which are set free. Conjugation between ordinary individuals occurs also in the large marine genus *Noctiluca*, where it is of a complicated type and is followed by active sporulation. The next step in complication is that the conjugating individuals are more or less differentiated both from one another and from the ordinary or indifferent individuals of the species, differing in characters of body-structure and cytoplasmic detail, as well as in the constitution of the nucleus, which undergoes a process of maturation of the usual type. Such a condition is found in the few cases where conjugation has been observed in *Trypanosoma*, and the resulting zygote is described as at first without blepharoplast or flagellar apparatus, the former being formed anew from the synkaryon.

Finally, in the more highly specialised Mastigophora, both free-living and parasitic, a process of sporulation produces individuals which may be either male, female, or indifferent, that is to say non-sexual, in structural characters and in function. The male and female forms conjugate, while the indifferent forms develop without conjugation into the adult form. By specialisation of the gametes, resembling that seen amongst Coccidia

and Hæmosporidia, the male gametes produced from a mother-cell or gametocyte may be very numerous and minute; while the female gametes, on the contrary, are bulky and inactive, and do not arise by division of the mother-cell, but each gametocyte becomes simply a female gamete after certain nuclear changes, the process of sporulation being in abeyance. The extreme of differentiation is seen when, as in many Sarcodina and Sporozoa, the individuals which give rise by sporulation to the indifferent isospores are distinct from those which produce the sexual anisospores. When the various types of individual are combined in a colony, as in *Volvox*, we find (1) individuals which produce the isospores or so-called parthenogonidia, (2) individuals which produce male gametes or microgonidia, and (3) individuals which become the female gametes or macrogonidia. The last-named are large non-flagellated individuals resembling Metazoan ova.

The Mastigophora are divisible into four subclasses:—(1) Flagellata (Euflagellata), which may be defined as having simply the characteristics of the class, without the special characters which distinguish the following subclasses. (2) Dinoflagellata or Peridiniales of botanists, an abundant group of Mastigophora, chiefly marine, in which there are typically two flagella, one flagellum running for a short distance in a longitudinal groove in the tough body-envelope and then projecting freely from the body, the other flagellum running round the body in a circular transverse groove. The movements of the transverse flagellum have a certain resemblance, at first sight, to those of a ring of cilia, for which the transverse flagellum was originally mistaken, hence the group was formerly termed Cilioflagellata. The nutrition is holophytic. (3) Cystoflagellata (Rhynchoflagellata), to include the marine genera *Noctiluca* and *Leptodiscus*, pelagic forms in which the adventitiously enlarged body consists chiefly of gelatinous substance with a relatively small amount of protoplasm. (4) Silicoflagellata, including various marine genera (*Stephanosphaera*, etc.) parasitic in Radiolaria and having a peculiar lattice-like silicious skeleton. Of these four sub-classes, only the Flagellata possess special medical interest, on account of their frequently parasitic habit, and the remaining three subclasses need not, therefore, be further dealt with.

The Flagellata are an exceedingly abundant group, occupying all possible situations in life where sufficient moisture exists to float their tiny bodies, and are differentiated into a great number of species and genera. At present but little is known of their complete life-histories, even in the case of the very commonest forms. Hence it is scarcely possible in the present state of our knowledge to form conclusions as to the true affinities and inter-relationships of the generic types, and no two authorities agree in their modes of classifying them. The classification adopted here must not be regarded, therefore, as in any way final, but merely as a temporarily convenient mode of grouping these very plastic organisms.

The Flagellata are commonly divided into:—(a) *Choanoflagellata*, in which the flagellum is always single and is surrounded at the base

by one, sometimes two, collars. This group contains a number of interesting free-living forms, mostly occurring in fresh water, but, as there are no parasitic forms known, it is unnecessary to concern ourselves further with this group here. (b) *Lissoflagellata*, in which the flagellum may be single or multiple, and a collar is not present, though there may be an undulating membrane. The *Lissoflagellata* comprise three orders:—

1. *Monadidea*—forms usually small and of simple structure, with one or more flagella, with or without a definite region of the body at which food is ingested, but in any case without a distinct œsophagus. Contractile vacuole if present, simple, opening direct to the exterior. Without chromatophores, stigmata, pyrenoids, etc.; holozoic, saprophytic, or parasitic.

2. *Euglenoidina*—specialised forms, typically with definite mouth-aperture and œsophagus, with complex vacuole-system, often with chromatophores, stigmata, pyrenoids, and paramylum-bodies; holozoic, holophytic, or saprophytic. Examples—*Astasia*, *Euglena*.

3. *Phytoflagellata*—exclusively holophytic forms without mouth or œsophagus, with chromatophores, etc. Examples—*Chlamydomonas*, *Volvox*. This group is sometimes placed as a distinct subclass of the *Mastigophora*.

All forms of parasitic flagellata hitherto known are referred to the first of the above-mentioned orders, namely, the *Monadidea*. This order may be conveniently subdivided into the three sub-orders *Pantastomina*, *Protomastigina*, and *Polymastigina*.

1. The sub-order *Pantastomina* differs from the other two in having no specialised region of the body for the ingestion of food, which is taken in at any point on the surface. It includes two interesting types of structure: first, the so-called *Holomastigoda*, represented by the genus *Multicilia* Lauterborn, in which the numerous flagella are scattered evenly over the surface of the body; secondly, the *Rhizomastigoda*, represented by *Mastigamœba* F. E. Schulze, and similar forms, in which the body is completely amœboid and bears one or two flagella. No parasitic forms are known as yet from this sub-order.

2. The sub-order *Protomastigina* includes forms with a specialised region for the ingestion of food—in those forms, that is to say, in which the nutrition consists of solid food-particles ingested by the organism. The flagella are not more than two in number. This sub-order, which contains the majority of parasitic flagellata, is commonly subdivided into monomastigote, paramastigote, heteromastigote, and isomastigote forms. The artificiality of such a method of classification is seen from the fact that in the single family *Trypanosomatidæ* it is necessary to include both heteromastigote and monomastigote forms. Well-known free-living examples of this sub-order are the genus *Monas* and the numerous allied genera, such as *Ecomonas*, *Amphimonas*, etc. The heteromastigote genus *Bodo* includes both free-living and parasitic forms; *Bodo lacertæ* Blochmann occurs in the gut of lizards, and to the same genus Künstler has referred a biflagellate species, observed by him in a single case from

human urine, under the name *B. urinaria* (*Plagiomonas urinaria* Braun, *Cystomonas urinaria* Blanchard). The most important parasitic forms are the genus *Trypanosoma* and its allies, grouped together as the family *Trypanosomatidae*, the genus *Spirochaeta* and allied forms, and the genera *Herpetomonas* and *Crithidia*.

The family **Trypanosomatidæ** (*Trypanosomidæ* Doflein) has been founded to include various generic types, of which the most important are the well-known genera *Trypanosoma* Gruby and *Trypanoplasma* Lav. et Mesn. A feature common to all the members of the family is the possession of an undulating membrane, and with few exceptions they are hæmatozoic in habit, that is to say, parasites of the blood of vertebrates, occurring always, with the possible exception noted below (p. 36), free in the blood-plasma, and never within, nor attached to, the blood-córpuses.

A typical member of the genus *Trypanosoma* (Fig. 6) has a more or less spindle-shaped body, along one side of which runs the undulating membrane. At or near one extremity of the body is placed the blepharoplast (micronucleus, centrosome, kinetonucleus, basal granule).

The flagellum takes origin from the blepharoplast or from its immediate vicinity, and runs from this point along the free edge of the undulating membrane to the opposite extremity of the body, whence it usually continues its course as a free flagellum of variable length. The flagellum may, however, terminate its course with the undulating membrane, so that a free flagellum is absent. In either case it is convenient to distinguish the two extremities of the body as the flagellar and the antflagellar ends respectively. The undulating membrane may have a sinuous course and is usually much pleated. The flagellum in its course follows all the sinuosities of the margin of the membrane. The nucleus (macronucleus, trophonucleus) is a conspicuous structure placed usually near the middle of the body. The cytoplasm may contain various granulations, and sometimes a vacuole occurs in the vicinity of the blepharoplast, but these are features which are not constant, as a rule, even in individuals of the same species.

In *Trypanoplasma* (Fig. 7) the blepharoplast is of considerable size, and from it arise two flagella, one of which projects forward as a free anterior flagellum, while the other runs backwards down the body along the free edge of the undulating membrane, as in *Trypanosoma*. The arrangement of the flagella is therefore heteromastigote, and only differs from such a type as *Bodo* in that the

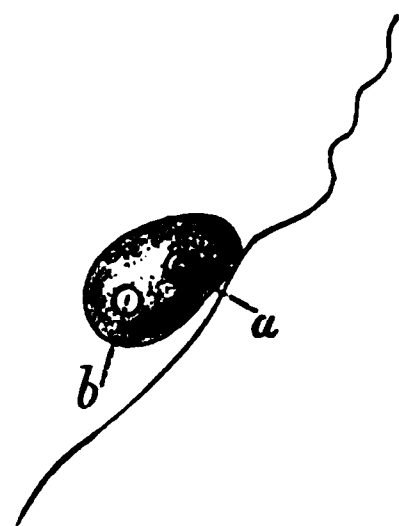


FIG. 4.—*Bodo lens* Müll., a free-living heteromastigote form; a, nucleus; b, contractile vacuole.



FIG. 5.—*Bodo urinarius* Kunstl. After Kunstler, from Braun.

posterior flagellum is adherent to the body by means of an undulating membrane.

A morphological comparison of *Trypanosoma* and *Trypanoplasma* suggests at once that the single flagellum of the former represents the posterior flagellum of the latter, in which case the flagellar extremity of a *Trypanosoma* is to be regarded as posterior, the antflagellar end as

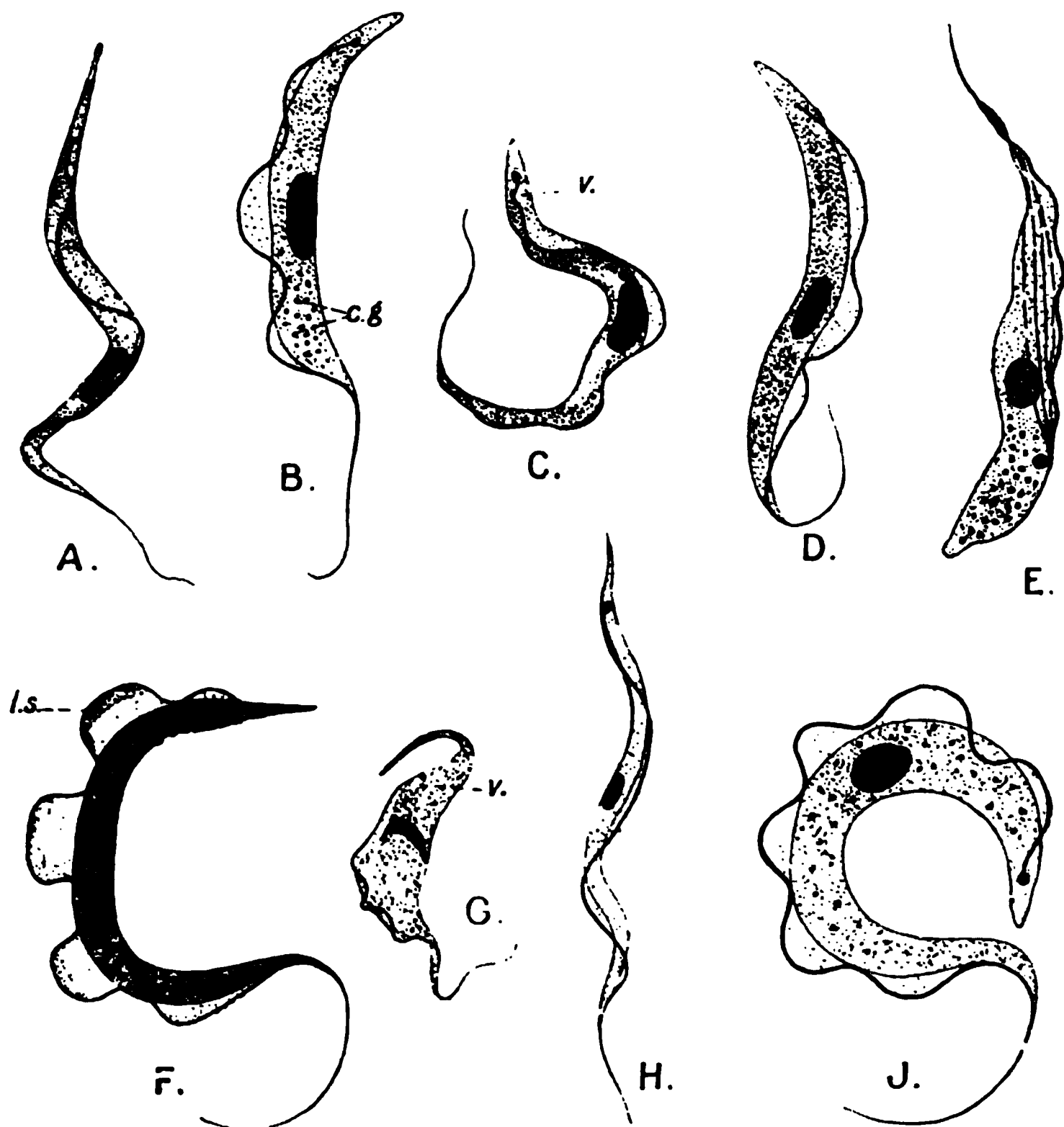


FIG. 6.—Representative mammalian, avian, and reptilian trypanosomes. A, *T. lewisi*, after Bradford and Plummer; B, *T. brucei*, after Laveran and Mesnil,  $\times 2000$ ; C, *T. gambiense*, after Bruce and Nabarro; D, *T. equinum*, after Laveran and Mesnil,  $\times 2000$ ; E, *T. nocturne*, after Schaudinn; F, *T. arinum*, after Laveran and Mesnil; G, Hanna's trypanosome from Indian pigeons; H, *T. ziemni* (*Spirochaeta ziemni*), after Schaudinn; J, *T. damonir*, after Laveran and Mesnil,  $\times 2000$ ; c.g., chromatoid granules; v., vacuole; l.s., fold or striation. From Woodcock.

anterior. On the other hand, there are developmental data which indicate a morphological interpretation of the body precisely the opposite to the foregoing. In a normal *Trypanosoma* from the blood of its vertebrate host, the blepharoplast is always nearer to the anti-flagellar extremity than the nucleus, and the undulating membrane extends along the greater part of the length of the body; but in certain developmental forms the reverse is the case, the blepharoplast may be

situated nearer to the flagellar end than is the nucleus, and the undulating membrane may be short, extending over less than half the length of the body, or may even be temporarily absent. Such forms occur both naturally in the invertebrate host and in cultures; if they are to be interpreted as recapitulative of phylogeny, they indicate a derivation from a *Monas*-like form with a single terminal anterior flagellum, the origin of which, together with the basal blepharoplast, has been shifted backwards along the body, the course of the backward migration of the flagellum being marked by the undulating membrane. According to this hypothesis the flagellar end of a *Trypanosoma* would be regarded as morphologically anterior, which is the view taken by most writers.

The formation of a flagellum in a trypanosome has been described in detail by Schaudinn in *T. noctue* (see below, p. 40). From this author's observations it would appear to follow that only the free flagellum is a

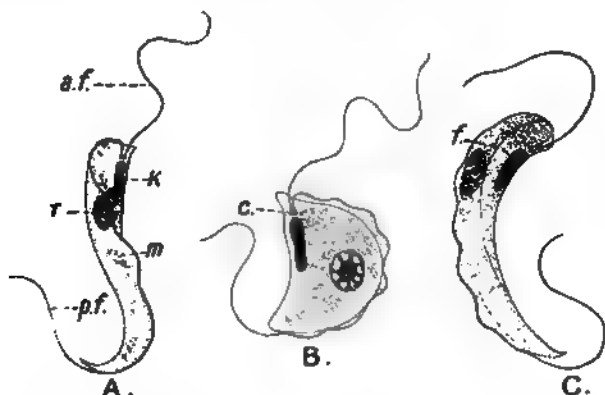


FIG. 7.—*Trypanoplasma borrelli* Lav. et Mesn., three varieties of the body-form. From Woodcock, after Léger.

true flagellum, comparable to that of an ordinary monad, while the marginal flagellum, that is to say the portion which forms the edge of the undulating membrane, is a structure of quite different nature, derived from the achromatic spindle of a nucleus dividing by mitosis. The free flagellum grows forward from a centrosome-like granule, and may therefore be regarded as anterior.

Some authors are of opinion that among trypanosomes two morphologically distinct types are to be found, in one of which the flagellum is anterior, while in the other it is posterior. Thus, Lube considers the trypanosomes of fishes to be derived from *Trypanoplasma*-like forms in which the posterior flagellum has persisted, and proposes for them the generic name *Haemulomonas* Mitrophanow, while the trypanosomes of mammals, in which the flagellum is regarded as anterior, are given a new generic name, *Trypanozoon*. Similarly, Woodcock (88) has proposed the name *Trypanomorphia* for *T. noctue*, in which the flagellum is regarded as anterior, while in other trypanosomes he regards it as posterior. It is



hardly possible at the present time to pronounce decisively on these questions, but from a comparative morphological standpoint it has been pointed out above that there are analogies from other flagellates in favour of an undulating membrane being formed by adhesion to the body of a posteriorly directed "Schleppgeissel." Observations on actual movements of trypanosomes do not help much towards deciding the point, as the direction in which the body moves is not always the same. In the case of the trypanosome of sleeping sickness, however, I was able to observe that when free from contact with blood-corpuscles and surrounding objects they were prone to move with the flagellum forwards, but that when pushing their way between the corpuscles in narrow spaces, they always progressed with the non-flagellated extremity forwards, using the flagellum apparently after the manner of a "Schleppgeissel."

The known species of *Trypanoplasma* are all parasitic in the blood of fishes. The very numerous species of *Trypanosoma* are all primarily blood-parasites in vertebrates of all classes, but they have the power in some cases of passing from the blood into the lymph or other serous fluids. Another genus referred to this family is *Trypanophis* Keysselitz, with a single species *T. grobbeni* (Poche), parasitic on certain species of Siphonophora (marine Hydrozoa). Like *Trypanoplasma*, *Trypanophis* has two flagella. The type-species of *Trypanosoma* is *T. rotatorium* (*Amœba rotatoria* Mayer = *Trypanosoma sanguinis* Gruby = *Undulina ranarum* Lankester) of the common frog. Lühe has proposed to retain the genus *Trypanosoma* only for the species parasitic in cold-blooded animals, but the name is used in this article in the wider sense.

The majority of species of *Trypanosoma* are not harmful to their hosts; but of special importance is a group of species occurring in mammals, and in many cases markedly pathogenetic—such are *T. brucei* Plimmer and Bradford, of the "Nagana" disease of horses and cattle in Africa (Fig. 6, B); *T. equiperdum* Doflein, of "Dourine" in horses; *T. evansi* Steel, of "Surra" in horses and cattle; *T. equinum* Voges, of "Mal de caderas" in horses in South America; and lastly, the human trypanosomes of Gambia fever and sleeping sickness, generally regarded as the same species under the name *T. gambiense* Dutton (Fig. 6, C). All the pathogenetic species just mentioned are remarkable for their very great morphological similarity, which renders them practically indistinguishable by structural characters, and it has been suggested that they are all merely races of a single species. In some of the pathogenetic species it has been clearly proved that they have natural hosts to which, by mutual adaptation, they are harmless. Thus *T. brucei* is found as a natural parasite of wild game (antelopes, buffaloes, etc.) in its native haunts in Africa, and *T. equinum* is similarly a natural parasite of the capybara (*Hydrochoerus*) in South America. To discover the natural host of the trypanosome of sleeping sickness is one of the greatest desiderata in the study of the etiology of this disease.

The pathogenetic properties of the trypanosomes mentioned depend

upon their power of adapting themselves to various hosts ; that is to say, when transferred either by biting insects or by artificial inoculation to certain animals other than those in which they naturally occur, they flourish exceedingly, it may be said abnormally, in the new host, and so work its destruction. An instructive comparison is furnished in this respect by the non-pathogenetic *T. lewisi* of the rat (Fig. 6, A). When rats are inoculated with this trypanosome, the parasites multiply rapidly for about eight days, then cease to do so, and pass into an adult resting stage, which gradually dies out, after which the rat is not again susceptible to the infection. Moreover, *T. lewisi* is not known to flourish in any other animal except the rat. In the guinea-pig it can maintain its existence for a certain time, but does not multiply. On the other hand, when *T. brucei* of "Nagana" disease (Fig. 6, B) is introduced into the blood of a rat, it multiplies continually, until shortly before the inevitable death of the host there may be as many trypanosomes as red corpuscles in the blood, if not more ; and this trypanosome can flourish in a similar manner in many other mammalian hosts.<sup>1</sup>

It has been proved that, with one exception, all the species of *Trypanosoma* and *Trypanoplasma*, that have so far been investigated carefully, have a second host, an invertebrate animal of some kind, which acts as an intermediary between the vertebrate hosts. The one exception is *Trypanosoma equiperdum* of "dourine," which is alleged to be transmitted directly from a sick animal to a healthy one by means of coitus. In all other cases the intermediary is a blood-sucking invertebrate, which in the case of trypanosomes parasitic on terrestrial vertebrates is most usually a dipterous insect, but in the case of those of aquatic vertebrates is commonly a leech. Further, in all cases hitherto studied, it is found that the trypanosomes undergo their sexual cycle in the invertebrate host alone, and never in the vertebrate host, on which account the invertebrate host is termed by some authorities the definitive host.

The main features of the development which are common to all types hitherto studied are as follows. The individuals of the species can be distinguished more or less easily into, first, indifferent forms, and, secondly, sexually differentiated forms, so-called male and female. All three types may multiply by fission, but this method of multiplication may be in abeyance in the fully developed male and female individuals. The three types can frequently be recognised in the blood of the vertebrate host, but they only become fully differentiated in the invertebrate host. In either host the ranks of the sexual individuals are recruited continually by differentiation of indifferent forms into males and females. These sexual forms may themselves become the gametes, or, as in *T. noctuæ* (see p. 35), are gametocytes from which the gametes arise.

The male trypanosomes are characterised by more slender form of

<sup>1</sup> A large trypanosome resembling *T. theileri* of the ox has recently been described by Kudicke from the blood of a monkey (*Cercopithecus*) which had been inoculated from a negro who was suffering from symptoms of trypanosome infection, but in whose blood no trypanosomes could be found.



body and greater length of free flagellum, features which make for the greater activity that is especially distinctive of the male type. The cytoplasm is clear and free from coarse granulations, and the nucleus is more or less compressed and drawn out, in correspondence with the slender body-form.

The female trypanosomes are distinguished by greater bulk and less activity. The cytoplasm may contain numerous coarse granulations, probably of the nature of reserve material, and the nucleus is more compact and rounded than in the males.

Of the three types, the males are generally the most delicate in constitution, and soon die off if they do not conjugate. The indifferent forms are more hardy than the males, but the most resistant of all are the females, on account of the reserve material stored up in their abundant cytoplasm. Under adverse conditions it may happen that all the male and indifferent forms die off, only the females maintaining their existence. A process of parthenogenesis may then take place in the surviving females, which consists in the nucleus going through certain changes involving a process of self-fertilisation, whereby the individual is set back, so to speak, into the indifferent condition. It then multiplies and repopulates the host, its descendants being differentiated again later on into males and females. Parthenogenesis of this kind may take place either in the blood of the vertebrate host, or in the gut of the invertebrate when the parasites have become reduced in number by long periods of starvation.

The sexual forms undergo before conjugation a process of maturation consisting of elimination of nuclear substance. The maturation may take place in the blood of the vertebrate (Prowazek), but in that case it is abortive and leads to no results. The general rule is for the maturation to take place in the gut of the invertebrate host, where alone conjugation can go on. The two matured gametes fuse completely, their bodies, nuclei, and blepharoplasts becoming amalgamated, each to each. The flagella and undulating membranes disappear, and the single blepharoplast produced by fusion is said to pass into the single nucleus of like origin, the whole constituting the complex synkaryon. The resulting zygote is a gregarine-like individual similar to the ookinete or vermicule stage of the malarial parasites (see p. 81). By heteropolar division of the nucleus a new blepharoplast arises, flagellum and undulating membrane are formed afresh, and the zygote becomes an ordinary trypanosome which commences a new vegetative cycle of generations.

In the foregoing paragraphs the principal stages of the normal life-cycle have been described. Numerous other phases and forms of trypanosomes are known, however, which cannot be considered to belong to the natural development of these organisms. Such are, first of all, the very numerous degenerative phases, for instance the so-called involution forms found in sick animals suffering from the effects of pathogenetic trypanosomes; and the plasmodial aggregations of *T. brucei* described by Plimmer and Bradford must be included in this category. None of

these degenerated forms are ever to be found in trypanosomes living in their natural hosts. A second series of similar forms is furnished by the development of trypanosomes in artificial media, forms so produced being often extremely unlike any known phases of the natural cycle. The cultural forms of trypanosomes are interesting for comparison with natural phases, as illustrating the effect of changes of medium upon the developmental mechanics of a plastic organism; but until the normal phases of the life-cycle are known, the cultural phases are without value from a zoological point of view.

There remains, however, an important phase or series of phases to be considered, which have been described as occurring normally in the life-cycle of at least one species, namely, the intracorpuseular or intracellular phases in the blood of the vertebrate host. The life-cycle of *Trypanosoma noctue* Celli and Sanfelice, as described by Schaudinn (75), furnishes

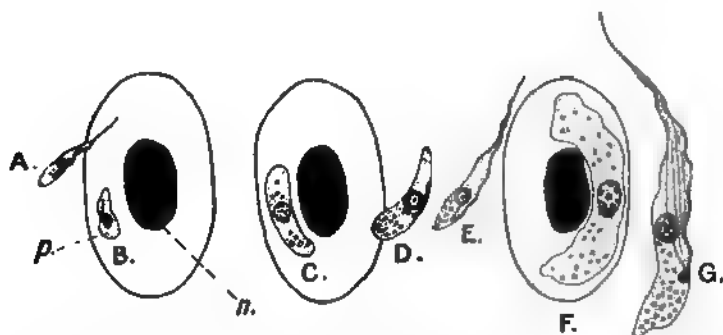


FIG. 8.—*Trypanosoma (Halteridium) noctue*, stages in the growth of an indifferent trypanosome in the blood of an owl. n, nucleus of red blood-corpuscle; p, intracellular parasite. In A a small trypanosome is shown entering a corpuscle, in B a young halteridium-stage is seen leaving the corpuscle to become a free trypanosome such as E; G, full-grown trypanosome. From Woodcock, after Schaudinn.

concrete examples of this, as well as of other important points in the life-cycle of a trypanosome. Some of the statements made by Schaudinn are very remarkable and require special consideration.

*Trypanosoma noctue* occurs in the blood of the little owl (*Athene noctua*), the invertebrate host which disseminates the parasite being the gnat *Culex pipiens*. The description of the life-cycle may be commenced conveniently with the minute trypanosomes introduced into the blood of the owl by the proboscis of the infected gnat; these may be either indifferent, male, or very young female forms, the full-grown female forms being too large to pass down the gnat's proboscis. The males very soon die off, but the indifferent forms multiply, and their descendants may become differentiated into male and female types. The young females grow up to become ordinary female forms, which by a process of parthenogenesis may become indifferent forms and multiply as such.

The point in which the development of *T. noctue* in the blood of its host is alleged to differ from all other known trypanosomes is that stages

during which the parasite is free in the blood alternate with stages in which it is intracorpuseular (Fig. 8). The young forms are described as attaching themselves by their flagella to red blood-corpuscles and then gradually penetrating into the latter, finally lying within the corpuscle by the side of the nucleus. In this condition the parasite is totally devoid of locomotor apparatus, the flagellum and undulating membrane have disappeared, and the blepharoplast has become closely applied to the nucleus. The trypanosome has now become changed into the form of hæmatozoic parasite long known from birds under the name *Halteridium* (see under *Hermosporidia*, p. 91). According to Schaudinn the halteridium-stage is succeeded again by a free trypanosome-stage; the parasite develops its locomotor apparatus afresh in the manner which will be described below, and breaks out of the corpuscle, which is but little injured by it, to become free in the plasma once more. The two forms have a regular alternation; the free trypanosome-stages are to be found at night occur-

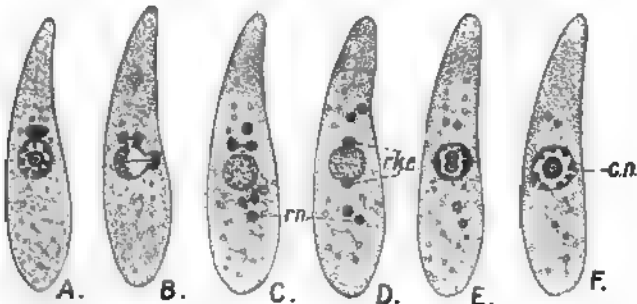


FIG. 9.—*Trypanosoma acuter*, parthenogenesis. r.n., residual nuclei; r.k.e., reduced kinetonuclear elements; c.n., compound nucleus, comparable to that of an ookinete (compare Figs. 10 and 13, A). From Woodcock, after Schaudinn.

ring chiefly in internal organs, when the host's temperature is at its lowest; the halteridium-phases are found by day in the peripheral circulation. The entire period of growth from the youngest to the full-grown trypanosome, with its regular alternation of phases, lasts over six days and six nights, in the case of an indifferent form, but the female forms grow much more slowly. When full-grown the trypanosomes multiply by rapid fission to form numerous small trypanosomes which start upon a fresh period of growth. The gametocytes, however, do not leave the corpuscle but require to be taken up by a gnat in order to undergo development within it. If this does not occur, the male gametocytes die off, but the female gametocytes may multiply by parthenogenesis.

A gametocyte about to multiply by parthenogenesis (Fig. 9) may, after a period of scanty nutrition, have absorbed the reserve materials stored up in its cytoplasm, which becomes more or less vacuolated. It has no trace of locomotor apparatus, and the blepharoplast is closely applied to the nucleus (Fig. 9, A); the latter contains a distinct karyosome. The nucleus first divides with disruption of the karyosome, budding off, as

it were, by so-called heteropolar karyokinesis, a small nucleus (Fig. 9, B), which goes through two successive divisions forming three small nuclei, two of which, as "polar bodies," commence to degenerate. The blepharoplast also divides twice, and two of the division-products begin likewise to degenerate. Thus at this stage the body contains one large and six small nuclei or chromatic bodies; of the latter, four are

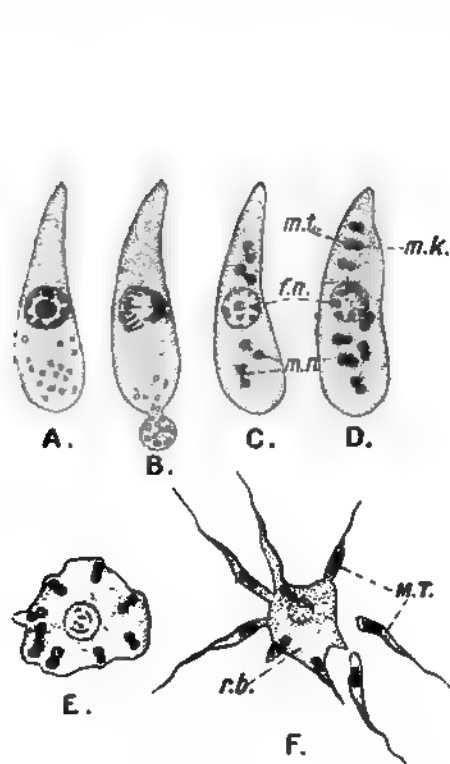


FIG. 10.—*Trypanosoma noctue*, development of microgametocytes and trypanosomes of male characters from an ookinete. *m.n.*, male nuclei; *f.n.*, degenerating female nucleus; *m.t.*, male trophonucleus; *m.k.*, male kinetosome; *M.T.*, male trypanosome. *r.b.*, residual body. From Woodcock, after Schaudinn.

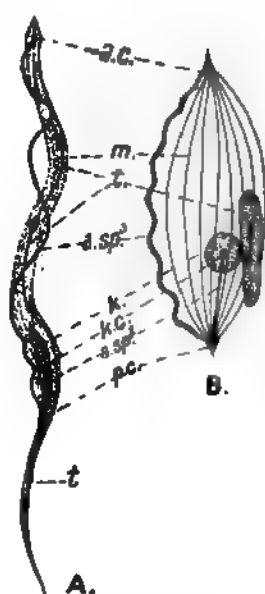


FIG. 11.—*Trypanosoma noctue*. A, male gamete; B, diagram of its structure; *c.*, nucleus (trophonucleus); *k.*, blepharoplast (kinetosome); *k.c.*, its centrosome; *a.sp.*, *a.sp.*, second and third axial spindles, the third forming the flagellar border of the undulating membrane; *a.c.*, *p.c.*, anterior and posterior centrosomes; *m.*, myonemes; *t.*, tail-like prolongation of the body. From Woodcock, after Schaudinn.

degenerating and are ultimately absorbed, while two persist in a normal condition (Fig. 9, C, D). The two persisting small nuclei penetrate from opposite sides into the large nucleus and fuse together to form its karyosome (Fig. 9, D, E, F). The animal has now become in form and structure exactly similar to the zygote (Figs. 10, A, 13, A), and, in the manner that will presently be described for the latter, it forms its locomotor apparatus and becomes a trypanosome of indifferent type, or, it may be, gives rise to male or female forms.

In order to undergo their normal development the full-grown gametocytes require, as has been said, to be taken up by a gnat into its stomach with a meal of blood. The two forms of individual have distinct characters, which may be summed up by saying that in the males the nucleus is more, the cytoplasm less developed, while in the females the reverse is the case, the cytoplasm being full of granules of reserve material, while the nucleus is relatively small. Both forms contain melanin-pigment similar to that of the malarial parasites. In the male gametocytes the pigment-grains are finer, in the female coarser. This pigment is cast out from the body in the stomach of the gnat, in the males before gamete-formation, in the females after fertilisation.

In the male gametocytes the large nucleus with which the blepharoplast has become fused divides by heteropolar mitosis into a larger and a smaller nucleus (Fig. 10, B). The larger nucleus begins to degenerate, the smaller one divides up to form eight small nuclei (Fig. 10, C). Each of these divides again into a couple of sister-nuclei, which remain close together and become different in structure, one sister-nucleus becoming the trophic nucleus, the other the blepharoplast, of the future gamete (Fig. 10, D). The eight couples become arranged at the periphery of the body, round the central large degenerating nucleus (Fig. 10, E). The protoplasm at the surface of the body grows out into eight small projections, each containing one of the couples of differentiated sister-nuclei, and each such projection is constricted off from the main body, at the same time forming a locomotor apparatus and becoming a male gamete (Fig. 10, F). The rest of the body of the male gametocyte, with the remains of the large nucleus, dies and becomes disintegrated.

The fully formed microgamete (Fig. 11) has an elongated slender body containing a long drawn-out nucleus which consists of four chromosomes. Behind the middle of the body lies the large blepharoplast, described as containing eight chromosomes. Behind the blepharoplast, but some way from the extreme hinder end of the body, lies a minute granule or centrosome, and another is situated at the extreme anterior end of the body. Between the two centrosomes runs the flagellum, which stands out from the body as the free edge of an undulating membrane. A free flagellum is lacking. The undulating membrane contains eight myonemes or contractile threads.

The female gametocytes become female gametes, going through a process of maturation as soon as they arrive in the stomach of the gnat. The body rounds itself off, and bursts the remains of the blood-corpuscle (Fig. 12). The blepharoplast is closely applied to the nucleus, and the two together divide twice to form two reduction-nuclei. At the end of this process the ripe macrogamete contains a pronucleus and two degenerating "polar bodies" each consisting of a nucleus and a blepharoplast in close apposition. The pronucleus contains four chromosomes. The macrogamete (Fig. 12) does not form a locomotor apparatus, but remains a spherical, inert body which is sought out and fertilised by the microgamete, which fuses with it. The locomotor apparatus of the micro-

gamete breaks down, and it brings to the macrogamete its nucleus with four chromosomes and its blepharoplast with eight; the latter, however, undergoes two reducing divisions. The two nuclei fuse by means of a "fertilisation-spindle" similar to that of the Coccidia and Haemosporidia; the male and female blepharoplasts place themselves at the two poles of the spindle. The nucleus rounds itself off, and the two blepharoplasts pass from the poles to the centre and fuse together. The process of conjugation is now complete, and the zygote becomes a motile vermicule or ookinete (Fig. 13, A), which may develop in one of three ways. It may become a trypanosome of indifferent or of female character, or it may give rise to eight small trypanosomes of male character, in the manner already described for the development of the microgametes (Fig. 10). Male forms, if produced, soon die off in the gut of the gnat, as they do in the blood of the owl.

In the development of a trypanosome of indifferent character (Fig. 13), the first step is the casting off from the body of a portion of the protoplasm containing the melanin-pigment, and the various reduction-nuclei, to wit, the two polar bodies formed by maturation of the female gametocyte, and the two reduction-nuclei formed by the male blepharoplast, as already described. The next step is the formation of the locomotor apparatus.

The nucleus or synkaryon of the zygote consists, as has already been said, of elements derived both from the trophic or principal nuclei and from the blepharoplasts of the gametes. Each set of structures contains eight chromosomes. The blepharoplast elements form a karyosome lying in the centre of the nuclear complex, and the karyosome contains a central granule. The eight chromosomes of the karyosome become mixed with those of the nucleus proper. Then the central granule divides into two and initiates a heteropolar mitosis, whereby the synkaryon becomes divided into a larger and a smaller nucleus (Fig. 13, C). The former represents the new trophic nucleus, the latter the new blepharoplast. From now onwards the formation of the locomotor apparatus proceeds in the same manner as at any other stage of the life-cycle; that is to say, the following description of the subsequent course of events will apply equally to the manner in which the locomotor apparatus arises each time a halteridium stage becomes a trypanosome in the owl's blood, or when a female multiplies by parthenogenesis, or during the development of the male and female types of trypanosomes (Fig. 13, D-H).

Each of the two unequally sized nuclei contains a central granule or centrosome connected with that of the sister-nucleus by a fine thread (Fig. 13, D). The smaller nucleus divides by a heteropolar division

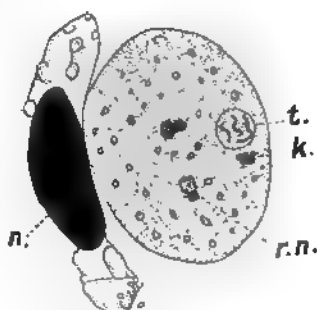


FIG. 12. — *Trypanosoma noctua*, a ripe macrogamete liberated from its host-cell. n, nucleus of disintegrated blood-corpuscle; t, reduced trophic-nucleus; k, reduced kinetocell-nucleus; r.n., degenerating reduction-nuclei. From Woodcock, after Schaudinn.

into two nuclei of unequal size, each also containing central granules connected together by a thread (Fig. 13, E). The smaller of these two nuclei, that is to say the smallest of the three nuclei present in the body, travels to the periphery and divides by mitosis to form a nuclear spindle, which runs in a longitudinal direction, and is again heteropolar in structure, the anterior end being smaller than the posterior (Fig. 13, F). This mitosis is not completed, but persists in the stage of the spindle,

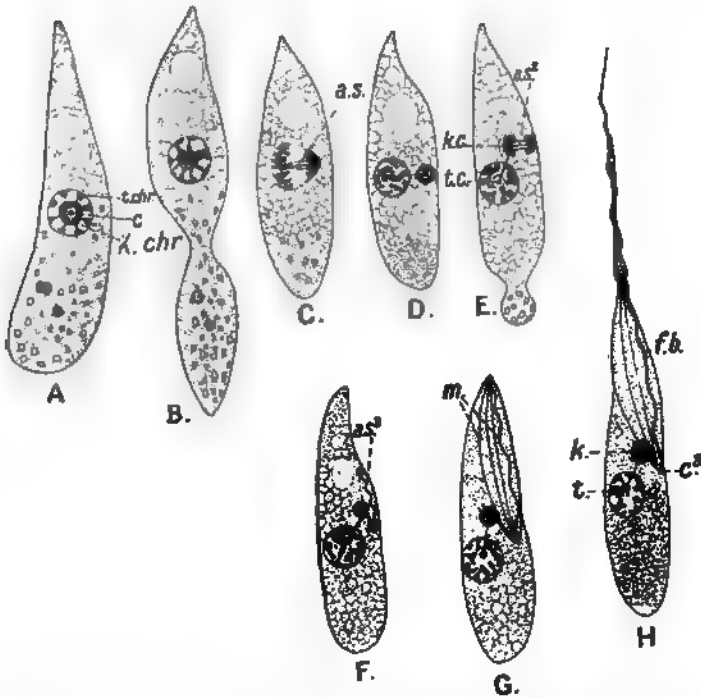


FIG. 13.—*Trypanosoma nectur*, development of a trypanosome of indifferent character from an ookinete. *t.chr*, eight chromosomes of the principal nucleus (trophonucleus); *k.chr*, eight chromosomes of the kinetoplast (kinetoneucleus); *c*, centrosomic granule; *a.s.*, first, *a.s.*<sup>2</sup>, *a.s.*<sup>3</sup> second and third, axial spindles; *t*, trophonucleus; *t.c.*, its centrosome; *k*, kinetoneucleus; *k.c.*, its centrosome; *m*, myonemes, *f.b.*, flagellar border of undulating membrane, *c.*, its proximal centrosome. After Schaudinn, from Woodcock.

of which the achromatic elements consist of an axial filament and eight mantle-fibrils connecting the two centrosomes. The achromatic spindle places itself at the surface of the body (Fig. 13, G), and is converted bodily into the locomotor apparatus (Fig. 13, H). The axial filament becomes the marginal flagellum (Fig. 13, *f.b.*), it places itself at the edge of the spindle to form the edge of the undulating membrane, and its anterior end grows past the anterior centrosome to form the free flagellum. The eight mantle-fibrils of the spindle form the eight myonemes of the undulating membrane. The chromosomes disappear, apparently. Thus,

the complete locomotor apparatus consists of the undulating membrane with its marginal flagellum and eight longitudinal myonemes, all converging at their extremities, both anteriorly and posteriorly, into a centrosome; from the anterior centrosome arises the free flagellum; the posterior centrosome is connected by a thread, of the same nature as the marginal flagellum, with the central granule of the blepharoplast, and the latter in its turn by a similar thread with the central granule of the principal nucleus. Schaudinn's discoveries reveal a complication of the locomotor apparatus hitherto unsuspected in such minute objects.

In the case where the zygote develops into a trypanosome of female character, the synkaryon divides by heteropolar mitosis into a large and a small nucleus. The small nucleus then divides into eight small nuclei, just as in the male gametocytes (Fig. 10, C, D). In this case, however, the eight small nuclei degenerate, and the large nucleus persists and forms the locomotor apparatus in the manner already described. Schaudinn regards indifferent trypanosomes as hermaphrodite in character, and the first step in their differentiation is interpreted as a sorting out of male and female nuclear substances, one or the other persisting or degenerating according to the sex to be produced.

The fertilisation and subsequent differentiation of the zygotes takes place in the stomach of the gnat, and is succeeded by active multiplication of the trypanosomes. As the blood becomes digested they pass into a resting stage and attach themselves to the epithelium of the stomach. When the gnat takes in a second feed of blood they are aroused and enter on a second period of multiplication and attach themselves in clumps to the epithelium of the anterior region of the stomach, which is regenerated at each meal. When at the third meal this epithelium is cast off, the clumps of attached trypanosomes are carried with it into the proctodæum. A few individuals are left, however, attached to the wall of the stomach in various places, and these, if they be females, may multiply later by parthenogenesis and repopulate the gut of the gnat. The clumps of trypanosomes in the proctodæum break through its wall at the junction of the ileum and colon, and so get into the body-cavity. Some may then penetrate the ovaries and cause hereditary infection of the next generation. Most of the trypanosomes, however, pass into the heart, and are carried forward with the blood-stream to the region round the pharynx, where they collect in great numbers and break through into the lumen of the pharynx. At the next meal, the fourth counting the one at which they were taken in, the parasites pass down the proboscis into the blood of the vertebrate host and recommence a new cycle. It need only be added that when the conditions are unfavourable the trypanosomes undergo agglomeration, always by their flagellated ends in this species; and that after long periods of starvation, all forms may die off except the females, which persist and under better conditions repopulate the gut of the gnat by parthenogenetic reproduction.

The development of *Trypanosoma noctua*, as set forth above from



Schaudinn's descriptions, is remarkable in several points. First of all there is the alleged occurrence of non-flagellated halteridium-stages, not known in any other trypanosome, though the so-called piroplasmoid stages of the Leishman-Donovan bodies perhaps furnish an example of analogous phases. The consequences of this discovery, as they affect the hæmosporidia, will be discussed below. Secondly, we may call attention to the remarkable details of structure described in the undulating membrane and its mode of formation. The bearing of these statements on the general morphology of the trypanosome-body has been discussed on p. 30. On both these points more confirmatory evidence is urgently needed before it is possible to form any final judgment upon these questions.

In the development of *T. lewisi* of the rat, Prowazek found no intracellular stages. In this form the sexual individuals become the gametes; there are no differentiated gametocytes, nor are the macrogametes so specialised as to be inert ovum-like bodies, as in *T. noctuae*. This author found appearances interpreted by him as parthenogenesis of female individuals.

As possibly close allies of the *Trypanosomatidæ*, and by some authors even referred to this family, must be mentioned the peculiar forms referred to the genus *Spirochaeta* Ehrenberg, often confused with bacteria of the genus *Spirillum*; hence the diseases caused by them are still generally termed spirillooses collectively. The organisms in question have the appearance of minute slender threads, wavy or spirally twisted in form.

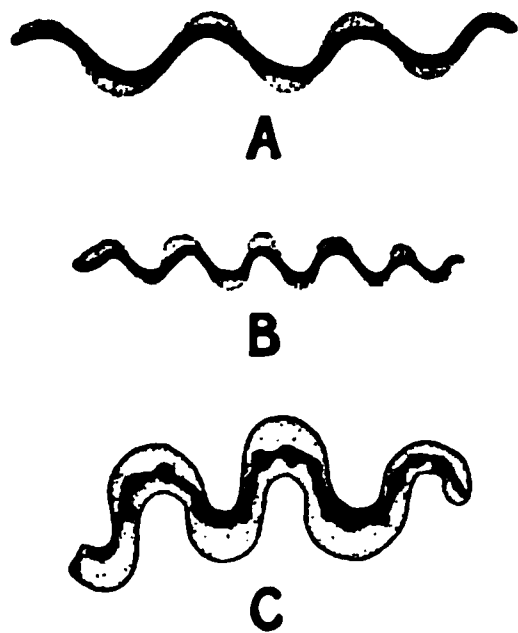


FIG. 14.—A and B, *Spirochaeta refringens* Schaud.; C, *S. plicatilis* Ehrenb., extremity of a large specimen. After Schaudinn.

They differ from a true *Spirillum* in the body being flexible, enveloped only in a soft periplast, and not in a firm cuticular cell-membrane, in possessing, in typical forms, an undulating membrane, and in lacking flagella. At the present time, however, many forms are referred to the genus *Spirochaeta* to which the foregoing definition does not apply in all its details, and the process of separating all these species into new genera has begun already. The original species to which the name *Spirochaeta* was applied is *S. plicatilis* Ehrenberg, a free-living form, which will therefore remain as the type of the genus *Spirochaeta* in all future applications or limitations of the name. *Spirochaeta*

*plicatilis* (Fig. 14, C) is of fairly large size and has blunt, rounded ends. The undulating membrane is very distinct, but there is no trace of flagella. The nuclear apparatus consists of a thread-like structure, running in the long axis of the organism, which Schaudinn regards as corresponding to the locomotor nuclear apparatus of the trypanosomes, while the ordinary nucleus is represented by chromidial granules surrounding the thread. The points considered by Schaudinn (76) to be characteristic of a true

*Spirochæta* are the undulating membrane, the absence of flagella and the blunt ends. If, however, these characters, especially the last, are to be taken as diagnostic of the genus, it is obvious that many forms at present termed indiscriminately *Spirochæta* will have to be referred in the future to distinct genera and receive other names.

Many important parasitic forms have been referred to the genus *Spirochæta*. We may begin with considering one for which Schaudinn (75) has described a complete life-cycle in detail, namely *Spirochæta ziemanni* (*Harmamæba ziemanni* Laveran, *Leucocytozoon ziemanni* Lühe), which occurs together with *Trypanosoma noctua* in the blood of the owl *Athene noctua*, and is also transmitted by the intermediary of *Culex pipiens*. The indifferent spirochætes in the blood of the owl resemble in structure, according to Schaudinn, minute slender trypanosomes with nucleus, blepharoplast, undulating membrane, and flagellum (Fig. 6, H). They are parasites of the white blood-corpuscles and of the erythroblasts. Multiplication is by fission in the longitudinal direction (Fig. 15), and two sister-individuals produced in this way may remain connected by their hinder ends to form in union a long slender snaky filament (Fig. 15, B), which can move with either end forward. The spirochætes may, by rapid division, become so small that they are only visible when agglomerated into rosettes. Schaudinn considers that these minute forms would pass through a Chamberland filter, as does the invisible micro-organism of yellow fever. The spirochætes may also pass into a resting stage in which they become *Piroplasma*-like, but with two chromatic bodies, a larger and a smaller, as in the Leishman-Donovan body (see p. 50). When the acute stage of the infection is passed, the minute indifferent forms begin to develop into sexual forms, gametocytes, which in comparison to the indifferent forms are of gigantic size, so large, in fact that they can only partially penetrate into the leucocytes or erythroblasts, to which they attach themselves by one extremity (Fig. 16). The gametocytes are typical trypanosome-like individuals. The male gametocyte passes into a resting stage without locomotor organs, and from this stage, if taken up by the gnat, arise the eight microgametes by a process of sporulation. The macrogametocyte also passes into a resting stage, and in the gnat's stomach it becomes freed from the remains of the cell to which it was attached, rounds itself off, and goes

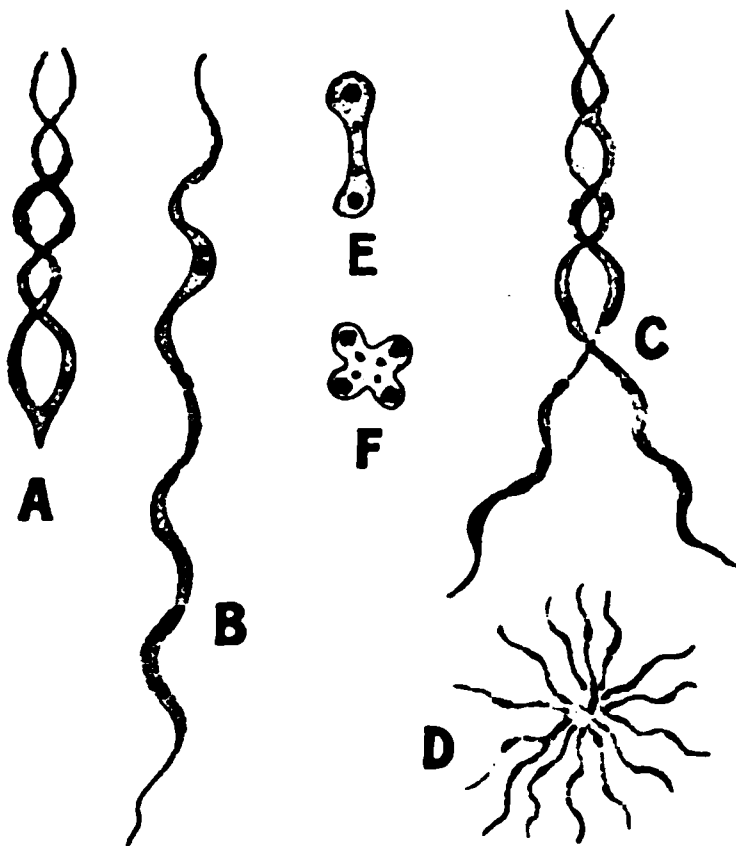


FIG. 15. — *Spirochæta ziemanni*. A, spirochæte dividing; B, the division nearly complete, the two daughter-individuals in a line; C, further division of two daughter-individuals connected as in B; D, agglomeration of minute spirochætes; E, F, resting stages of forms similar to B and C respectively. After Schaudinn.

through a process of maturation of the usual type, after which it is ripe for fertilisation as a mature macrogamete. Fertilisation (Fig. 17) in the usual manner by a microgamete produces a zygote which becomes a motile vermicule, which in its turn grows greatly in length, and becomes coiled into a compact mass, its nuclei at the same time multiplying by division. Finally, the zygote by a process of sporulation forms an immense number of spirochaetes, which swarm over the Malpighian tubes and intestine of the gnat, and multiply by fission in the same way as in the blood of the owl. The parasites pass forward in the blood-stream to the

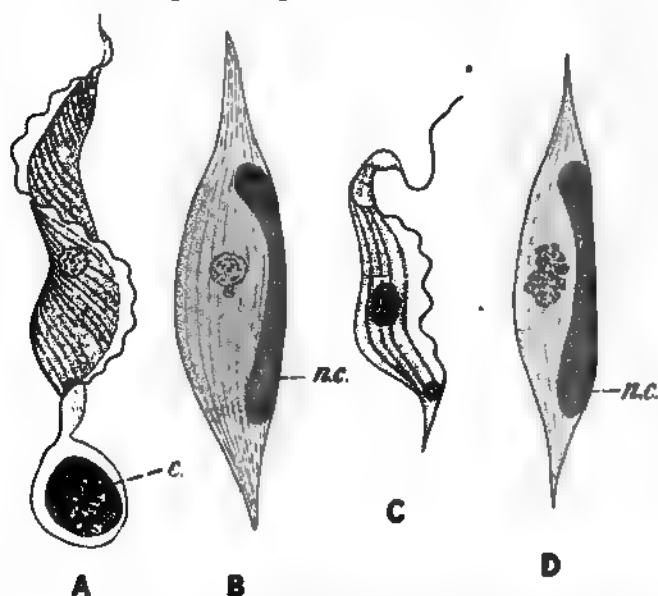


FIG. 16.—*Spirochaeta ziemannii* (Hirromachi z. Laveran, *Leucocytozoon* z. Lühe) gametocytes. A and B, female gametocytes, A with, B without, locomotor apparatus; C, trypanosome-like male gametocyte; D, male gametocyte after loss of locomotor apparatus, the nucleus commencing to divide up; c, host-cell; n.c., nucleus of host-cell. After Schaudinn.

pharynx, and are introduced by the proboscis of the gnat into a fresh avian host.

It was suggested by Schaudinn, when he made known these data relating to the development of *Spirochaeta ziemannii*, that all other spirochaetes would be found, when examined carefully, to be in like manner closely allied in structure and development to true trypanosomes. Schaudinn, however, abandoned this opinion, and considers that *S. ziemannii* is far removed from typical spirochaetes such as *S. plicatilis* Ehrenberg or *S. refringens* Schaudinn (Fig. 14, A, B), from which it differs in having pointed extremities and a free flagellum. The same applies also to an important group of spirochaetes parasitic in the blood of mammals and birds, of which the most important or best-known species are *Spirochaeta obermeieri* Cohn (*S. recurrentis* Lebert) of human relapsing fever, *S.*

*anserina* Sakharoff of geese and other anserine birds, and *S. gallinarum* Marchoux and Simond of fowls. At the present time it is far from settled whether these forms are to be referred to the Protozoa or to the Bacteria. Even essential matters of fact are in dispute in the most recent memoirs dealing with them. Thus, *S. gallinarum* is, according to Borrel and Laveran, shewn to be a bacterium of the family Spirillaceae by its "incontestable" transverse division, its numerous flagella arising from all parts of the body, and the absence of an undulating membrane, of a circumscribed nucleus, or of a centrosome. On the other hand, Prowazek (68) asserts the same species to be a Protozoön allied to *Trypanosoma*, on the ground that it possesses a distinct undulating membrane and that the division is longitudinal, that it is not plasmolysed by solutions of NaCl and alkalis, and that it exhibits occasional cell-parasitism; flagella are declared to be absent, the appearance seen by Borrel being explained as contractile fibrils split off ("abgelöste Myophane"). Between such flat contradictions further research must decide. Koch (36) and Zettnow, however, were also unable to find any trace of trypanosome-like structure in the spirochæte of African relapsing fever, regarded by Koch as identical with the European *S. obermeieri*, and both authors describe the division as transverse. Zettnow further confirms the discovery of Borrel, that the body of a spirochæte (*S. gallinarum* and *S. obermeieri*) is beset by numerous flagella. The many conflicting statements seem to indicate that at the present time the term spirochæte is applied in a chaotic and promiscuous manner to three or four distinct types of organisms; first, to true species of the genus *Spirochæta*, type *plicatilis*; secondly, to forms such as *S. ziemanni*, which are in reality minute trypanosomes; thirdly, to organisms of the type of *Treponema pallidum*, described below; and, fourthly, to organisms which perhaps are not protozoa at all. It should be mentioned in this connexion that Marchoux and Simond are of opinion that the hitherto invisible micro-organism of yellow fever also "belongs to the family of the Spirilla," as was suggested by Schaudinn on the analogy of *S. ziemanni*.<sup>1</sup>

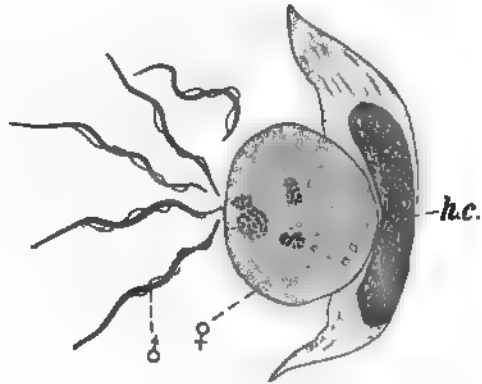


FIG. 17.—Fertilisation of *Spirochæta ziemanni*. ♂ male gamete; ♀ female gamete, containing the two pronuclei, i.e. nucleus and bi-plaroplast, each with eight chromosomes, and the two reduction-nuclei; h.c., remains of host-cell. After Schaudinn.

<sup>1</sup> Novy and Knapp are also of opinion that *Spirochæta obermeieri* and allied forms are to be regarded as bacteria and not protozoa; these authors propose the name *S. duttoni* for

The hæmatozoic spirochaetes are, like other blood-parasites, transmitted to new hosts by blood-sucking invertebrates. European relapsing fever is conveyed chiefly, apparently, by the bed-bug. The spirochaetes of fowls are conveyed by fowl-ticks of the genus *Argas*. The parasite of African relapsing fever is also conveyed by a tick, *Ornithodoros moubata*, and passes through two generations of its invertebrate host, the infection being given by larval ticks born of parents that acquired the infection originally. Koch (35) has investigated the development within the tick and found great numbers of spirochaetes in the ovary (Fig. 18, B), but these were quite similar to the forms in the blood, and did not shew any developmental stages such as were described by Schaudinn for *S. ziemanni*. Prowazek (68) describes *S. gallinarum* as passing into a resting stage by tying itself into a knot.

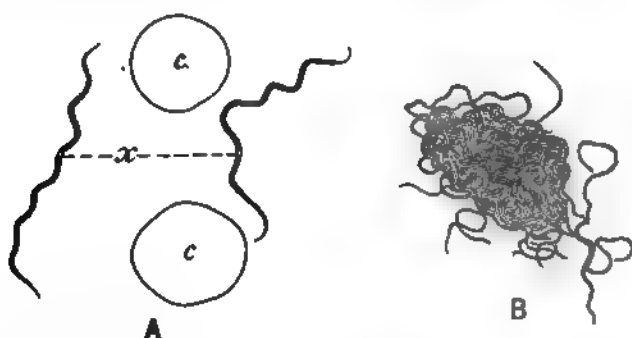


FIG. 18.—Spirochaete of African tick fever. A, two specimens from the blood; B, a clump of spirochaetes from the egg of the tick; c, c, blood-corpuscles in outline; x, a clear space in the spirochaete, regarded by Koch as indicating transverse fission. After Koch.

The parasite is also capable of penetrating the blood-corpuscles, and may assume the resting condition within them.

Other well-known species of *Spirochaeta* are *S. buccalis* Cohn and *S. dentium* Koch from the human mouth. A classified list of all known *Spirochaetae*, with their diagnostic characters, is given by Blanchard (4).

To the genus *Spirochaeta* has been referred also the recently discovered agent of syphilis under the designation *S. pallida* Schaudinn, and that of yaws under the name *S. pertenuis* Castellani. These species differ, however, from a typical spirochaete in the following points: The body is corkscrew-like, and shews numerous sharp, fine coils, which vary from ten to twenty six in number, and are preformed, that is to say, are not the result simply of the animal's wriggling movements; an undulating membrane cannot be made out, but appropriate methods reveal a slender prolongation, interpreted by Schaudinn as a flagellum, at each of the pointed tapering ends of the body (Fig. 19). Hence the parasite of syphilis has

the parasite of African tick fever, considering it to be distinct from *S. obermeieri*. Breinl (Liverpool School of Tropical Medicine, Mem. xx) comes to the same conclusion as Novy and Knapp, and proposes the same name for the parasite.

been placed in a distinct genus, *Spiromonas* (Vuillemin), but as this name is pre occupied, it has been altered to *Trepomona* by Schaudinn. The specific name *pallidum* is taken from the very slightly refringent nature of the body in life, and the difficulty with which it can be stained in preparations, properties which render the detection of the parasite very difficult. The minute organism is very active, moving with one or the other end of the body forwards, and at the same time rotating on its principal axis, or bending the body sideways. In deeply situated syphilitic lesions, *Trepomona pallidum* alone occurs, but in ulcerated surfaces there is commonly found associated with it another species, distinguished by its darker form and smaller number of twists on the spiral body, which Schaudinn has given the name *Spirocheta refringens* (Fig. 14, A, B).

Statements relating to finer structure and development of *Trepomona pallidum* have been put forward by Krzyształowicz and Siedlecki, who find that the body of the parasite is contractile, and can become thereby much shorter and thicker, with its curves less sharp, and at the same time more refringent, but the pointed extremities remain a distinctive feature

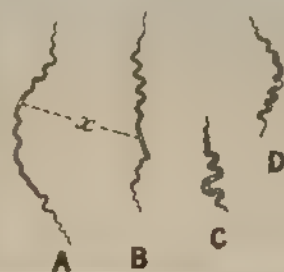


FIG. 19.—*Trepomona pallidum*. A and B, ordinary forms, C and D, contracted forms, a clear space, regarded as representing the nucleus. After Krzyształowicz and Siedlecki.

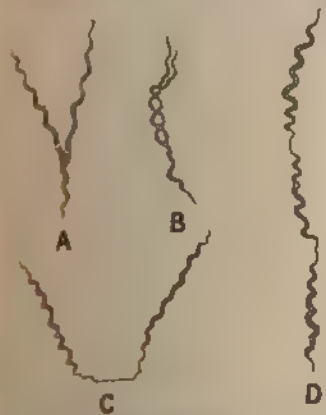


FIG. 20.—*Trepomona pallidum*. A, B, and C, ordinary forms, D, after fission. D, three individuals connected together as the result of fission. After Krzyształowicz and Siedlecki.

(Fig. 19, C, D). At some point, generally not far from the middle of the body, it is seen that for a short distance the body is straight, or nearly so, and very slightly thickened, and in this region a clear spot can be observed, which is regarded as the nucleus. The ordinary method of reproduction is by fission in a longitudinal direction (Fig. 20). The fission may for a time stop short of completeness, with the result that the two sister individuals may remain connected by their ends, and then may either be twisted up together or placed in the same line, forming a spirochete of great length. Sometimes more than two individuals are connected in this way by their ends. In addition to the ordinary individuals, the two Polish authors

describe also forms which they consider as sexual individuals. These are first, thicker spindle shaped forms with few bends, which the authors consider trypanosome like and propose to name *Trypanosoma*

*luis* (Fig. 21), although the minuteness of the organisms makes it impossible to recognise the undulating membrane and other details of trypanosome-structure; secondly, minute spirillum-like forms which appear to arise by segmentation of long thread-like forms with several nuclei (Fig. 22, A-D). The former are regarded as macrogametes derived each by growth of single *Treponema*-individuals; the latter, as microgametes formed by a process akin to sporulation from an individual with multiple nuclei. Conjugation (Fig. 22, E, F) between the two forms was observed in a single case "in materials taken from a very large primary ulceration which was beginning to cicatrise spontaneously." The authors suggest that the zygote passes into a resting stage and becomes transformed into some sort of cyst or spore, which is carried away in the circulation to other

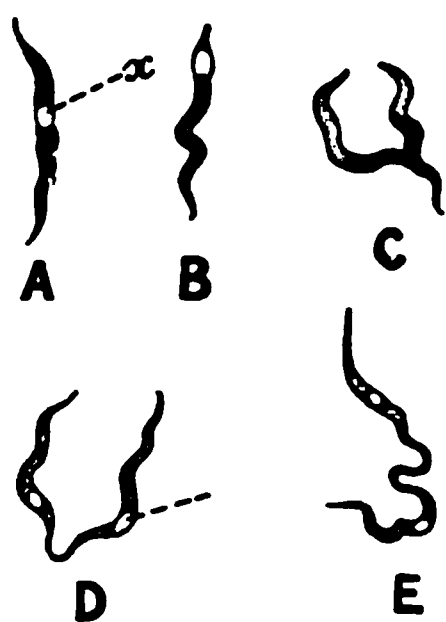


FIG. 21. — *Treponema pallidum*, female forms ("Trypanosoma luis"). A and B, ordinary individuals; C, D, and E, binary fission; x as in Figs. 18 and 19. After Krzysztalowicz and Siedlecki.

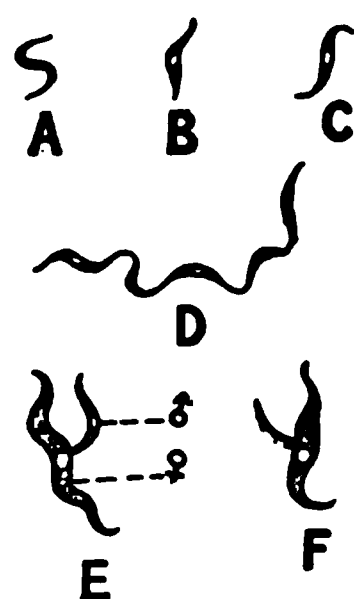


FIG. 22. — *Treponema pallidum*. A, B, and C, male gametes, derived from an elongated individual by multiple transverse fission as in D; E and F, conjugation of a male (♂) and female (♀) gamete. After Krzysztalowicz and Siedlecki.

parts of the body and gives rise to new spirochætæ which produce the secondary lesions. Other bodies of an enigmatic nature are described by the authors, whose observations urgently need confirmation. A possible stage in the life-cycle of this parasite is the problematic *Cytorhyctes luis* Siegel described below (p. 113).<sup>1</sup>

The transmission of *Treponema pallidum* from one host to another by the contagion of coitus, without an intermediate host, affords a suggestive analogy to the case of *Trypanosoma equiperdum* of "dourine," in which the infection is brought about in a similar manner.

In close proximity to the *Trypanosomatida*, but distinguished from them by lacking an undulating membrane, come various species of Flagellata parasitic, for the most part, in the digestive tracts of insects. Such are

<sup>1</sup> An additional contribution to the etiology of syphilis, published since this article was completed in MS., is the memoir of Mr. E. de Korte, "On Certain Bodies present in the Chancre in the Condyloma, and in the Blood during Secondary Syphilis" (*Practitioner*, June 1906).

the various species referred to the genera *Herpetomonas* Sav. Kent and *Crithidia* Léger.

In *Herpetomonas* (Fig. 23) the body has the form of a flattened rod, sometimes slightly dilated near the anterior end, from which the flagellum arises. The type-species is *H. muscæ-domesticæ* Burnett from the intestine of the common house-fly. According to Prowazek (63) the flagellum of *H. muscæ-domesticæ* is double, the two flagella being connected by a delicate membrane for some distance from their origin. In all other species that

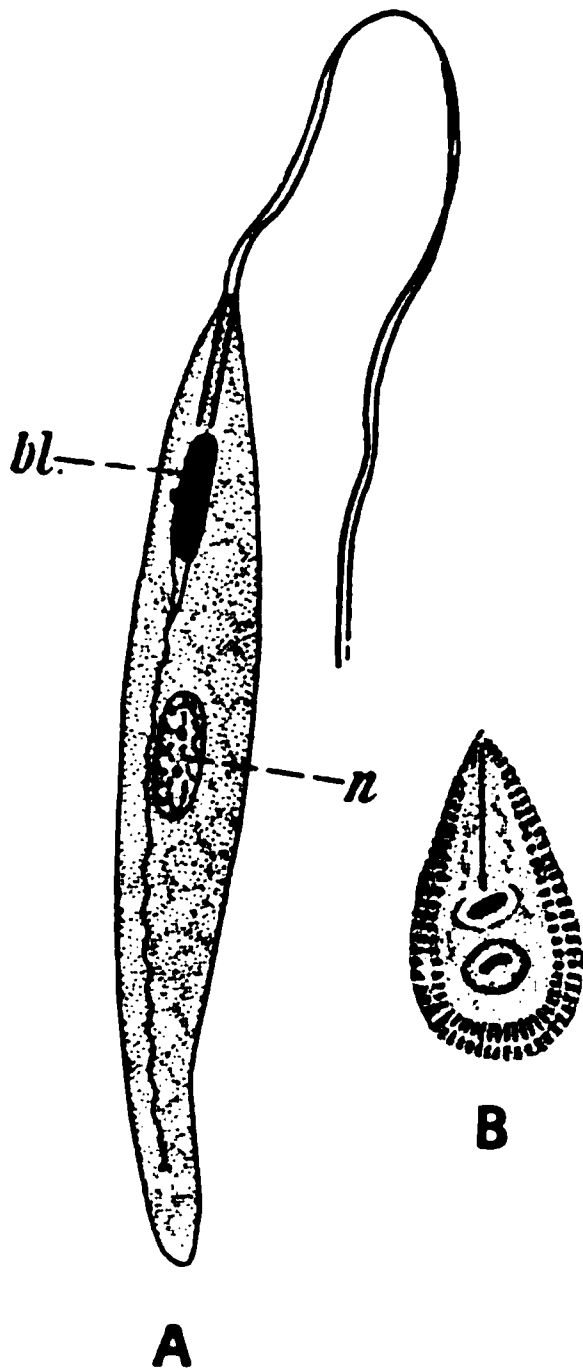


FIG. 23.—*Herpetomonas muscæ-domesticæ* Burnett. A, ordinary motile individual; B, resistant cyst; n, nucleus; bl, blepharoplast. After Prowazek

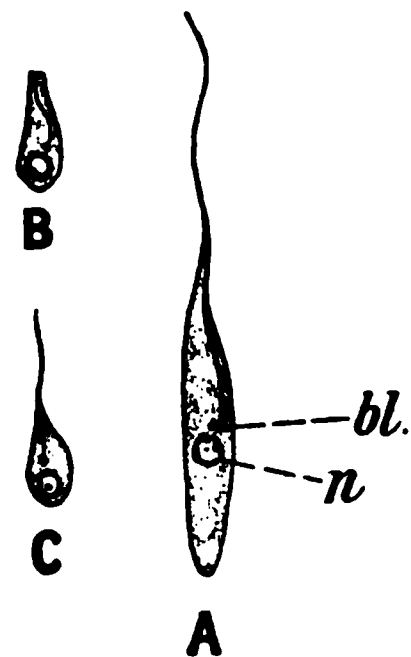


FIG. 24.—*Crithidia minuta* Léger. A, ordinary motile individual; B and C, young forms; B, without flagellum. After Léger.

have been referred to the genus *Herpetomonas* the flagellum is described as single, a difference from the type-species which is probably of generic value. In *H. muscæ-domesticæ* Prowazek found that the infection was conveyed partly by the formation of resting cysts, which are cast out of the gut and then swallowed accidentally by other flies, and partly by the hereditary method, through the parasites penetrating into the ovaries of their hosts. As stated below, the flagellated form of the Leishman-Donovan parasite has been referred to the genus *Herpetomonas*.

In *Crithidia* (Fig. 24) the body is more pear-shaped with the anterior end



pointed, the single flagellum arising from a blepharoplast situated near the nucleus. Examples are *C. minuta* Léger from the gut of *Tabanus tergstinus*, and *C. fasciculata* Léger from the gut of *Anopheles maculipennis*. The fact that both these insect hosts are of blood-sucking habit, and the considerable resemblance that the parasites themselves shew to some of the developmental forms of trypanosomes, are sufficient to arouse the suspicion that these species of *Crithidia* are simply developmental stages of blood-parasites. As yet, however, the life-cycle is not known in any of these forms.

In the sub-order of the Flagellata at present under discussion must be included, finally, certain human parasites, first, those known generally as the "Leishman-Donovan bodies"; secondly, those generally referred to as the parasites of oriental sore. The Leishman-Donovan bodies are found invariably in certain organs of the body, but mainly in the greatly enlarged spleen, in kala azar and similar diseases occurring in various parts of the tropics, especially in India, but also in China, Egypt, and tropical Africa. The parasites of oriental sore are found in the granulation-tissue of certain skin lesions which are of widespread occurrence in the tropics, and are known by various local names such as Aleppo boil, Delhi sore, Frontier sore, etc. In spite of the very great similarity, amounting to morphological identity, between the bodies occurring in kala azar and in tropical sore, there are good grounds for regarding the parasites in each case as distinct from one another. In India, for instance, their geographical range is different and their pathological effects are not the same; in the one case the parasites produce a general or systemic disease, in the other only a local lesion. Since all the developmental data known concerning these organisms have been worked out so far only in the case of the Leishman-Donovan bodies of kala azar, the following account applies to these parasites alone.

The *Leishman-Donovan* bodies have been the subject of much controversy, as regards both questions of hypothesis and matters of fact. They occur in immense numbers in the liver, spleen, and bone-marrow, and more sparingly in various other organs of the body. Unlike the parasites of tropical sore, they are not found in ulcers of the skin in cases where there is no general infection. The parasites are typically intracellular (Fig. 25); occasionally free forms are found, perhaps as the result of the dissolution of the host-cells, but parasites so liberated are probably soon taken up again by other cells. According to Christophers (16, 17) the cells which harbour the parasites are of two classes, leucocytes and cells of endothelial nature; the latter become greatly modified and distended by the parasite, and give rise to the large macrophages of the spleen and liver-cells which may each contain as many as 150 to 200 of the parasites. Inclusion in the cells is not in any way harmful to the parasitic organisms, which are able to resist the action of the enclosing cell; their vitality is clearly shewn by the fact that in culture-media the parasites enclosed in cells undergo development in the same way as those that are free. In their immunity to intracellular digestion the Leishman-Donovan

bodies contrast sharply, according to Christophers, with true piroplasmata when captured by leucocytes.

A disputed point as regards the occurrence of these parasites relates to those occurring in the peripheral circulation. Donovan, whom Laveran and Mesnil (41, 42) confirm, described and figured them in

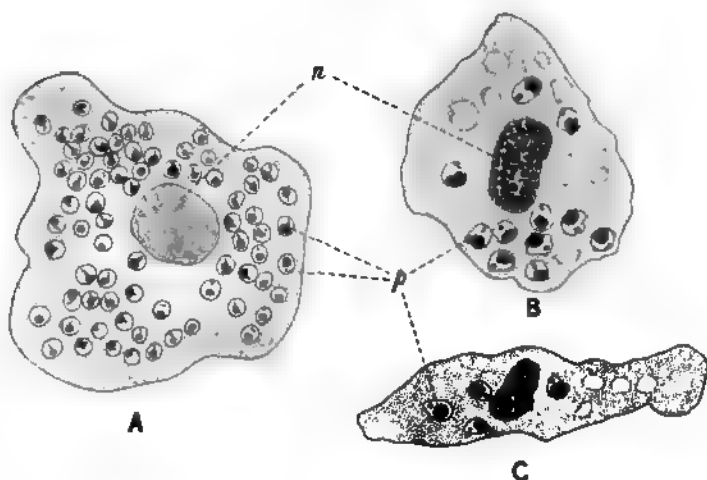


FIG. 25. —Leishman-Donovan bodies in cells. A, a macrophage. B and C, endothelial cells, containing the parasites (p); n, nucleus. After Christophers.

unaltered red blood-corpuscles in the general circulation, such forms being remarkable for their small size, and for having, like a true *Piroplasma*, a single chromatin mass. In the spleen Donovan found similar forms in unaltered corpuscles and others of ordinary size with two chromatin masses, in altered red corpuscles. Christophers (17), however, finds them only in leucocytes in the peripheral blood, and doubts the specific nature of the



FIG. 26. Leishman-Donovan bodies. A, three parasites in the ordinary condition, each showing two chromatin-masses; in one of them (more to the right) the smaller chromatin-mass shows a tail of chromatin proceeding from it; B, C, D, binary fission; E, multiple fission into three parts. After Christophers.

bodies in the red corpuscles, whether in the peripheral circulation, or in the spleen or bone-marrow.

The Leishman-Donovan bodies occurring in human tissues are minute rounded, ovoid, or pear-shaped bodies, measuring usually about  $2.5 \mu$  to  $3.5 \mu$  in the longest diameter, and  $1.5$  to  $2 \mu$  across the shorter axis of the body (Fig. 26, A). A distinct cuticle, which can be burst by pressure, limits

the surface of the body. The cytoplasm is often more or less vacuolated, and contains two distinct chromatin-masses or nuclei situated usually opposite to each other on the shorter axis of the body, and differing in size and appearance. The larger nucleus is compact, more or less spherical, and stains more faintly; the smaller one is generally rod-shaped, and stains very deeply. Sometimes a bridge of protoplasm joins the two nuclei across the vacuolated cytoplasm. In some cases Christophers observed a "tail" of chromatic substance proceeding from the smaller nucleus at right angles to its long axis; a similar structure was observed by James in the parasites of oriental sore. The parasites multiply by one of two methods. The most common method is simple binary fission (Fig. 26, B-D); in an individual not noticeably above the average size, the two nuclei divide, usually the larger one first, and then the body divides along the principal axis, that is longitudinally. A less common method is multiple fission (Fig. 26, E); the parasite grows in size and its two nuclei multiply to form three, four, or more of each kind, after which the cytoplasm becomes segmented round couples of dissimilar nuclei to form as many parasites as there are couples, each individual so produced being less than the ordinary size.

The reason for including the Leishman-Donovan bodies among the Flagellata is the remarkable fact, first discovered by Rogers (70), whose statements were confirmed and extended by Christophers (18) and Leishman (45), that when cultivated in suitable media and at moderate temperatures, the parasites undergo changes which result in their becoming *Herpetomonas*-like flagellate organisms. The period required for this development is about six days in ordinary cultures. Rogers found, however, that the development could be greatly accelerated by slightly acidulating the culture-media, a method to which he was led by an examination of the contents of the stomachs of various insects.

The first stage of the development of the parasite in cultures is a considerable enlargement of the body of the organism, combined with changes in the larger nucleus, which increases greatly in size, and becomes less compact in structure (Fig. 27; 2, 3). Next, the parasites multiply by fission at least twice, forming groups of two or four ovoid bodies. After this there appears in the neighbourhood of the smaller rod-shaped nucleus, a vacuole containing a substance which stains pink by the Romanowsky method (Fig. 27; 4, 5). The body now becomes pear-shaped, and the rod-shaped nucleus, with the vacuole, places itself near one pole of the body, usually the end which is narrower. The vacuole increases in size until it reaches the surface of the body. It then bursts or grows out from the body, forming a protruding fringe-like structure in which a definite flagellum makes its appearance, whether as a condensation of the fringe, or as a distinct formation in it, is not quite clear (Fig. 27; 6, 7). When fully formed the flagellum is relatively of considerable length, and takes origin near the rod-shaped nucleus, which is therefore the blepharoplast (Fig. 27; 8). The larger chromatic mass becomes the nucleus. The body of the organism now becomes considerably elongated, and sharply pointed at the

antiflagellar end, so that the flagellar extremity is always the blunter end of the body.

In many of the fully formed flagellate individuals Leishman found, in addition to the nucleus and blepharoplast, small grains of chromatin, generally in couples, a larger and a smaller together. This state of things is perhaps antecedent to the fact observed by him, that by a process of markedly unequal longitudinal fission, minute, slender, "spirillar" forms are split off from the large *Herpetomonas*-like individuals (Fig. 28). Sometimes more than one such spirillar form is split off simultaneously. At first the spirillar forms have no flagellum, but one is subsequently developed, and they then shew much greater mobility than the larger forms. No conjugation was observed, and no further

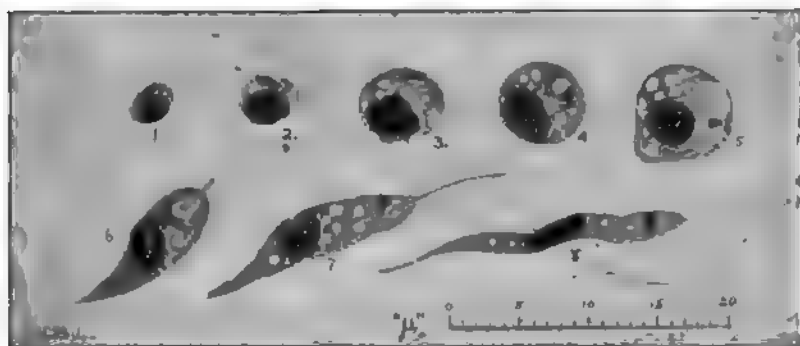


FIG. 27. Stages in the development of a flagellum in *Leishmania donovani*. 1, ordinary form of spleen parasite; 2, 3, growth of the parasite during cultivation, with vacuolation of the protoplasm; 4, 5, appearance and growth of the flagellar vacuole close to the blepharoplast; 6, rupture of vacuole and protrusion of the young flagellum in the form of a tuft or bunch of pink-staining threads; 7, growth of the flagellum, the thickened base being inserted in the collapsed flagellar vacuole; 8, fully developed flagellated form. Figures by Leishman.

development goes on in the cultures, the organisms ultimately degenerating and dying off.

No stages in the natural development of the parasite outside the human body have been observed, nor is it known by what agency the parasite is disseminated. The parasites of oriental sore could be taken up easily by the common house-fly, or any other insect which, like it, is attracted by open wounds or sores and draws nourishment from them. This does not, however, apply to the parasites of kala azar, for which it has been suggested that some blood-sucking arthropod acts as the intermediary, and Rogers has given reasons for suspecting the bed bug to be the agent of infection. If, however, this is the method by which kala azar is spread, it is unlikely that the invertebrate host acquires the infection in the form of the Leishman-Donovan body, since in this form the parasite is excessively scarce in the peripheral blood. The stages observed in cultures suggest the possibility that some minute spirillar or other form may be present in the blood, which, like the micro-organism of

yellow fever, has hitherto escaped detection, and is perhaps ultra-microscopic in size. Further light is needed on this point.

Many controverted opinions have been held as to the systematic position of the Leishman-Donovan parasites. Leishman, who first discovered them in films made post-mortem, considered them to be degenerated remains of trypanosomes, altered in shape and appearance by the death of the host. No trypanosomes have ever been found, however, in the blood of patients infected with these parasites, and the manner in

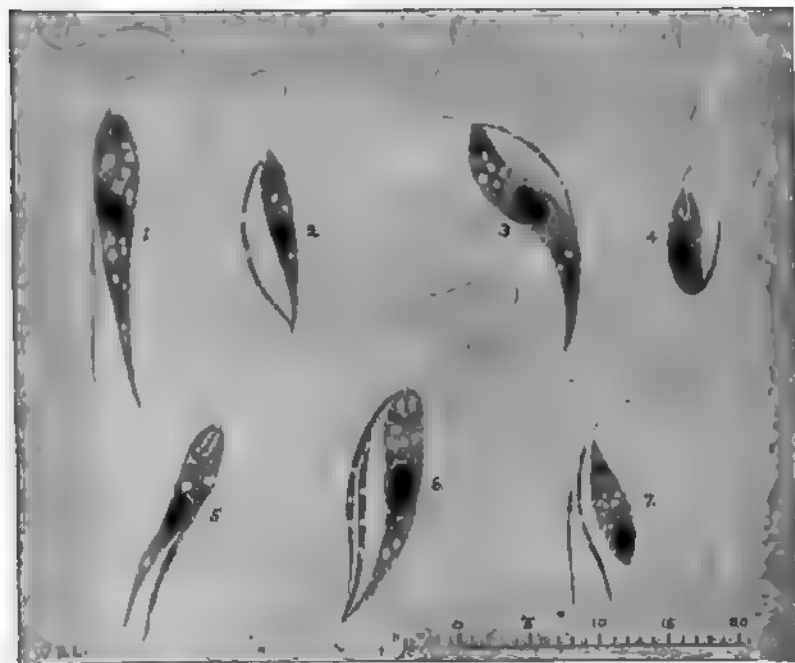


FIG. 28. Flagellated forms of *Leishmania donovani*, giving rise to spirillar forms by a process of unequal longitudinal fission. 1, 5, cleavage of single spirillar forms from the parent; 6, parasite giving rise to two spirillar forms; 7, two spirillar forms completely separated from the parent. Figures by Leishman.

which they multiply and develop shows that their vitality is in no way impaired. Laveran and Mesnil, to whom Donovan sent preparations, identified the parasite as a *Piroplasma*, and named it *P. donovani* (November 3, 1903). As stated on p. 51, however, the occurrence of the parasite in red blood-corpuscles is controverted, and, apart from the doubtful forms figured by Donovan, the parasite differs from a *Piroplasma* in possessing constantly two chromatic masses; moreover, no flagellate stages are known as yet in any true *Piroplasma*. Ross considered it a distinct form of protozoan parasite, and named it *Leishmania donovani* (November 14, 1903). Wright (89), while noting

certain resemblances to Microsporidia, proposed the name *Helcosoma tropicum* (December 1903) for the parasite of Delhi sore. Rogers considered at first that his discoveries confirmed Leishman's view that it was a trypanosome, but since the flagellate phase never shews any trace of an undulating membrane, he has proposed (71) to place the organism in the genus *Herpetomonas*. Leishman (45) has well pointed out, however, that forms known from cultures cannot be taken as decisive of its true affinities, since many cultural forms of trypanosomes, *e.g.* *T. lewisi*, lack all trace of an undulating membrane. Until, therefore, the natural flagellate stages, which are probably to be sought in some insect, have been found, and until also more facts are known concerning the exogenous or invertebrate cycle of *Piroplasma*, it is better to postpone judgment upon the position of this parasite, and to employ the generic name *Leishmania*, leaving it for the future to decide whether *Leishmania* will rank as a synonym or as a valid name. If the parasites of kala azar and oriental sore are generically identical but specifically distinct, as seems very likely, then the genus *Leishmania* will include two species: *L. donovani* (Lav. et Mesn.) and *L. tropica* (Wright).

3. The sub-order *Polymastigina* includes forms with more than two flagella, and with a special mouth aperture for ingestion of food. Many examples of this sub-order are found parasitic on man or other animals. None of them, however, are pathogenetic to man, and in consequence their life-histories have been very little studied, and the methods by which they obtain access to the human body are not known. The parasitic forms may be classified conveniently, following Doflein, into (a) *Tetramitidae*, with three or four flagella, all arising together; (b) *Polymastigidae*, with from four to six anterior flagella, and usually also two posterior flagella; and (c) *Trichonymphidae*, with very numerous flagella arranged in tufts.

In the family *Tetramitidae* the two most familiar genera are *Trichomastix* Blochmann and *Trichomonas* Donné. *Trichomastix* has three anterior flagella, and a large, backwardly directed trailing flagellum ("Schleppgeissel"); a species occurs in the gut of the lizard, *T. lacertae* Blochmann. In *Trichomonas* the posterior flagellum of the preceding genus is represented by an undulating membrane; familiar human parasites of this genus are *T. vaginalis* Donné (Fig. 30), occurring commonly in the vagina, sometimes also in the male urethra, and *T. hominis* (Davaine) (Fig. 29), from the intestine, and found also in the buccal cavity (Prowazek).

The family *Polymastigidae* includes, amongst other parasitic genera, the genus *Lambia* Blanchard, with the single species *L. intestinalis* (*Cercomonas intestinalis* Lambl, *Megastoma entericum* Grassi). *Lambia intestinalis* (Fig. 31) is an intestinal parasite of man and various animals, occurring normally in the duodenum and jejunum. It has a somewhat flattened body, pear-shaped in outline and symmetrical, with a large, sucker-like depression on the ventral surface, by means of which it can adhere to epithelial cells. It has four pairs of flagella, all directed backwards, one pair arising from the anterior border of the sucker, two pairs from the posterior border of the sucker, and one pair from the narrowed posterior

end of the body. It appears to be a parasite perfectly harmless to its host in all cases.

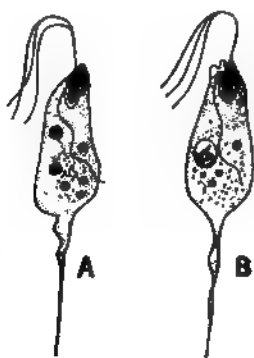


FIG. 29.—*Trichomonas hominis* (Davyne) from the human mouth. The three anterior flagella arise by a common stem which takes origin from the pear shaped nucleus, and the undulating membrane runs backwards from the point of insertion of the flagella. The body, prolonged posteriorly into a tail like process, contains numerous food-vacuoles, enclosing ingested micrococci. After Prowazek.



FIG. 30.—*Trichomonas vaginalis* Donne. After Blochmann, from Doflein.

The family *Trichonymphidae* includes curious forms from the digestive tracts of *Orthoptera* and *Termitula*. *Lophomonas blattarum* Stein is a

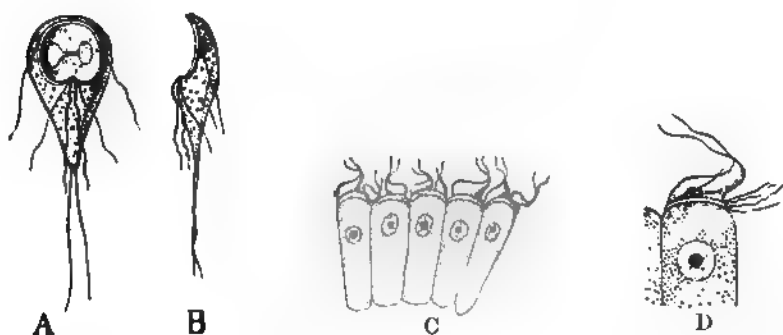


FIG. 31.—*Lashliea intestinalis*. A, from the ventral side; B, from the left side; C, attached to epithelial cells; D, a cell with parasite attached, more highly magnified. After Grassi and Schewiakoff, from Doflein.

species easily found in the gut of the common cockroach. The genus *Trichonympha* is sometimes referred to the Ciliata.

**Class III. Sporozoa.**—Endoparasitic Protozoa, without organs of locomotion, or for the capture or digestion of food, in the adult condition; reproduction always by some method of sporulation.

The Sporozoa are a difficult group to define, since the distinctive characters are principally of a negative order, the result of the peculiar mode of life. Even the characteristic from which the name of the group is derived, namely, reproduction and dissemination by means of resistant spores, is shared by Protozoa belonging to other groups, and is not of constant occurrence in the sporozoa themselves. The most distinctive feature of the reproduction of the sporozoa is perhaps not so much the general occurrence of sporulation as that the simpler method of binary fission is practically in abeyance throughout the group, or at least is seldom found. Hence even the reproduction shews negative rather than positive characteristics. It is highly probable that the sporozoa are not a homogeneous group, but are rather to be considered as an assemblage of forms characterised by a common parasitic habit, and derived probably from at least two distinct ancestral sources. While one subclass, the Telosporidia, is probably descended from flagellate ancestors, the Neosporidia, on the other hand, shew unmistakable affinities with the Sarcodina.

As a general rule among the sporozoa, a given species is restricted to a definite species of host, or at least to a few closely allied species. The parasites occupy every possible situation in the bodies of their hosts. The mode of occurrence is not necessarily constant all through the life-history, but a given species may pass normally through different phases, as regards habitat. It is convenient, however, to distinguish three different modes of parasitic habit, each comprising minor categories. First in importance comes the *cytozoic* habit, in which the parasites are found within, or attached to, cells. This habit is often found as an antecedent condition to other modes of parasitism, and is perhaps to be regarded as the most primitive type of parasitism in the whole group. The second or *cœlozoic* habit comprises those forms which are found in the internal cavities of the body, such as the lumen of the digestive tract and its appendages, the body-cavity, the hæmocœle, or the cavities of the urinary and reproductive organs. Those found in the gut itself may be termed *enterozoic*, as a special subdivision of the cœlozoic category. Cœlozoic forms may be either *free* in the space they inhabit or *attached* in some way to its walls. The third category of parasitic habit is the *histozoic*, comprising those forms which penetrate into, and are parasitic upon, the tissues of their hosts, where they are found usually lodged between the cells when full grown, but in most, perhaps in all cases, the youngest forms are intracellular in habitat, and may in some cases remain so. A special and important category of parasites is seen in the *hæmatozoic* forms parasitic in the blood of vertebrates, which are in all cases primarily intracorpuseular in habitat, and only secondarily and temporarily free in the blood fluid. The sporozoa hæmatozoic in vertebrata are therefore to be regarded as a special category of the cytozoic type. On the other hand, the sporozoa found in the hæmocœle of invertebrates are to be regarded as typically cœlozoic forms.

The body of a sporozoön may be either naked, and then usually



amoeboid, or limited by a distinct cuticle and of definite form. Amoeboid forms are seen in some of the Hæmosporidia and in the Myxosporidia and Microsporidia. The amoeboid habit of the body is not connected, however, with locomotion, but, if it has any physiological significance, perhaps favours absorption of nutriment at the body-surface, or may in other cases serve for temporary attachment of the parasite to internal surfaces of the host. When the body is of definite form, it is primarily spherical, as is well seen in the cytozoic coccidia, which frequently have a very striking resemblance to an ovum. Most usually, however, and especially in cœlozoic forms, the body becomes drawn out and lengthened along a principal axis, and shews every possible variation of form from a more or less elongated ovoid to a slender worm-like form. Such a type is especially common amongst the gregarines, but appears also in other orders as more or less transient phases, which are frequently termed vermicules or are described as *gregarinoid*. In spite of possessing no visible organs of locomotion, both gregarines and the gregarine-like phases are often very active, and exhibit not only movements of contraction and flexion of the body, but also have the power of gliding rapidly forwards in the direction of the principal axis. While the first-mentioned class of movements can be explained without difficulty by the contractility of the superficial myonemes presently to be described, it cannot be said that an incontrovertible explanation of the peculiar gliding movements has yet been given. Two hypotheses have been put forward as to the cause of the gliding movement: first, that it is effected by the secretion and extrusion of a thread of gelatinous substance, which pushes the animal forward as it is formed (Schewiakoff); secondly, that the forward movement is due to successive wave-like contractions of the superficial contractile body-layer (Crawley).

The cytoplasm of a sporozoön is commonly differentiated into a superficial ectoplasm, hyaline in appearance and free from coarse granules, and an internal, usually coarsely granular, endoplasm. The ectoplasm may be further differentiated into an external protective layer termed a cuticle, periplast, or *epicyte*, and a more internal contractile layer or *myocyte* containing contractile fibrils or myonemes. In motionless forms, however, such as the coccidia and many gregarines, a myocyte-layer is not differentiated. The endoplasm is the seat of nutritive activity, and contains, besides various metaplastic products, the nucleus or nuclei.

In any sporozoön it is convenient to distinguish sharply between the nutritive and reproductive activities of the parasite, even when the two phases are not entirely distinct from one another during the life-history. A parasite during the nutritive or trophic phase, when it is absorbing nutriment from the host and growing at the expense of the latter, may be termed a *trophozoite*. As a result of the parasitic mode of nutrition, the trophozoites shew no organs for the digestion of food, such as food-vacuoles, and in a single instance only has a contractile vacuole been described in the entire class.

When a trophozoite has grown to a certain size, the process of repro-

duction begins. The sporozoa may be divided into two subclasses, by the relation of the trophic and reproductive phases (Schaudinn). In the first subclass, the telosporidia, the two phases are entirely distinct, and the parasite first feeds and grows to its full size before reproductive activity commences. Hence in this subclass the trophozoite always has a single nucleus until, having attained its limit of size, it ceases to be a parasite, properly speaking, and commences to reproduce itself. In the subclass neosporidia, on the other hand, the trophozoite usually commences its reproductive activity at a very early period of its growth, and from that time onwards growth and reproduction go on simultaneously. Hence in the neosporidia the trophozoite is uninucleate only in its earliest stage, and very soon becomes, and remains, multinucleate.

The reproduction, as has been said, takes almost invariably the form of sporulation, in which process also the two subclasses shew characteristic differences. In all cases alike the sporulation commences with the separation from the parent body of small uninucleate masses of protoplasm which may be termed generally spore-mother-cells. In the telosporidia, after rapid and repeated multiplication of the nucleus, the body breaks up into a number of spore-mother-cells, formed simultaneously by constriction off from the surface of the body of small masses of protoplasm round each of the nuclei, which have previously travelled to the periphery. The central portion of the body is left over as residual protoplasm which disintegrates and takes no further share in the development. In the neosporidia, however, in which multiplication of the nucleus commences early and proceeds continuously, the spore-mother-cells are formed in the interior of the body by concentration of the protoplasm round one of the nuclei, and spore-formation goes on continuously in this manner. Hence a typical neosporidian consists of a central mass of spores enveloped in a peripheral layer of growing protoplasm, while in a typical telosporidian, in which reproduction is complete, a number of peripherally situated spores are found surrounding a centrally placed mass of residual, disintegrating protoplasm. From the differences in their methods of sporulation, the two divisions here classified as telosporidia and neosporidia were named by Metchnikoff "*Sporozoaires Exosporées*" and "*Endosporées*" respectively.

From the spore-mother-cells mentioned in the preceding paragraph arise the spores, but in different ways in different cases. In the telosporidia not more than one spore arises from a spore-mother-cell, which may, therefore, be termed simply a *sporoblast*, using this term to denote in all cases the mass of protoplasm from which a single spore develops. In the neosporidia, however, at least two spores, often more, are formed commonly from a single spore-mother-cell, which is then distinguished as a *pansporoblast*, each pansporoblast giving rise to a definite number of true sporoblasts, from each of which a single spore is formed. The sporoblast, however formed, may, in the first place, simply become a spore without further change except perhaps one of form, remaining naked at the surface without any protective envelope. Such a spore may be termed generally

a *gymnospor*, though it may have other special names in special cases. In the second place, the sporoblast may produce at the surface of its protoplasm a protective coat of tough resistant material, and thereby become a body which, in a strict terminology, should be distinguished as a *chlamydospore* (Dauerspore, resistant spore), but which, by long usage, is universally termed a *spore* simply, such spores being especially characteristic of the sporozoa. By Johannes Müller such spores were termed "psorosperms," a name used by subsequent writers in various senses, but generally to denote all phases or orders of sporozoa, and hence diseases caused by sporozoa are often termed collectively psorospermoses.

The process of multiplication may end with the formation of the spore, but does not necessarily do so. In the telosporidia, the spore-protoplasm, whether naked or protected, may be further divided up to form sickle-shaped germs termed *sporozoites*<sup>1</sup> (falciform bodies, Sichelkeime), or without division may become a single such germ. Each sporozoite is a minute and active vermicule, which represents at the same time the consummation of the reproductive phase, and the commencement of a new trophic phase, in the telosporidia. Hence in this group the sporozoites correspond to swarm-spores and take the place, as it were, of the amœbulae and flagellulae of other groups of Protozoa. In neosporidia the spore-protoplasm does not, as a rule, produce sporozoites, but it is set free in most cases, apparently, as a minute amœbula. Finally, it should be stated that the sporulation in telosporidia may or may not take place within a cyst, and may or may not be preceded by conjugation. In neosporidia conjugation has not been observed with certainty. In the gametes of telosporidia we find every condition from complete isogamy to highly differentiated anisogamy.

From the preceding paragraph it will be seen that the spore-formation is highly specialised and diversified in character. This phase of reproduction is best considered in connexion with the mode of dissemination of these parasites, to which the variations observed in spore-formation are simply so many adaptations. Speaking generally, the sporulation may have one of two results, either to increase the numbers of the parasite within the host, or to bring about the infection of fresh hosts. Reproduction directed towards the first of the ends is termed *endogenous*, towards the second *exogenous*. It may be supposed that primitively the two methods of reproduction would have been similar in character, if different in results, as is still the case in many forms; but increasing complexity in the life-cycle and in the structural adaptation of its different phases brings about a generally prevailing dissimilarity between the endogenous and the exogenous cycles, the former being known as *schizogony*, the latter as *sporogony*. In telosporidia the former is always non-sexual, while the latter, in all cases accurately studied, is always connected with conjugation in some form.

<sup>1</sup> Many English authors spell this word *sporozoite*, apparently in imitation of the German spelling. It may be pointed out that the word was coined by a French writer and spelt as in this article.

In considering the modes by which fresh hosts are infected, it is well to separate first the special case of the order hæmosporidia, which, as blood-parasites of vertebrates, are disseminated, like the hæmatozoic flagellates, by the intermediary of an invertebrate host, a blood-sucking arthropod or leech. Here the endogenous, non-sexual schizogony is found in the vertebrate host; the exogenous, sexual sporogony in the invertebrate host alone. In the inoculative method of infection characteristic of the hæmosporidia no resistant spores, but only gymnosporos are found at any stage in the life-cycle, since the parasite is never outside the sheltering body of the one or the other of its two hosts. In all other sporozoa, so far as is known, the method of infection is a casual or accidental one. Spores cast out from the body of the host are accidentally swallowed by a new host, in which they germinate. Thus the parasitic cycle starts from the digestive tract in all cases. In the casual method the parasitic germs must be exposed for a time to the vicissitudes of the outer world, and it is as a protection during this period that the characteristic spore-envelopes and cysts are developed, all to be dissolved up or cast aside when taken into the new host. Hence in sporozoa generally, the exogenous cycle is characterised by the formation of protective envelopes which in the endogenous cycle are quite absent, being quite unnecessary. Resistant cysts and spores characterise exogeny: gymnosporos, without cysts, characterise endogeny. The further multiplication of the parasitic germs within the spores is merely an instance of the prolific fertility which so frequently characterises parasitic life-cycles.

In many instances among sporozoa ordinary or casual infection is supplemented by hereditary or germinative infection, in which the parasites pass from one animal to its descendants through the reproductive organs. In the case best known, that of *Glugea bombycis* of the silkworm disease, resistant spores are formed in the ovum and germinate in the next generation. Instances of hereditary infection are of most frequent occurrence in hæmatozoic forms which are transmitted by an intermediate invertebrate host, and for such cases it may become the rule that the parasite passes through two generations of the invertebrate. For an enumeration of these cases see Mesnil [51].

Subclass I of the Sporozoa.—*Telosporidia*.—Trophic and reproductive phases distinct, alternating with each other; trophozoites uninucleate; sporulation of superficial type (hence Exosporées Metchnikoff); swarm-spore a sporozoite or falciform young.

Three orders are included in this division—the Gregarinoidea, Coccidiidea, and Hæmosporidia.

1. *Gregarinoidea*.—The gregarines are telosporidia characterised by a cirlozoic habitat, as well as by certain peculiarities in the reproduction (sporogony) presently to be described.

The gregarines include the largest and most differentiated of the sporozoa. As parasites they are not known to occur in any true vertebrate, although they occur not uncommonly in Prochordata

(Ascidians and Amphioxus). They are pre-eminently parasites of arthropods, but occur commonly also in worms and in echinoderms. In molluscs they are very rare. In all cases they appear to be very harmless parasites.

The gregarines are primarily parasites of the digestive tract, in which, in the earliest stages, the trophozoite is cytozoic, being attached to, or contained in, an epithelial cell of the gut (Fig. 32). When the host-cell is used up, the young trophozoite becomes coelozoic in habit. Either it drops back into the lumen of the digestive tract, which always occurs when the penetration of the host-cell is only partial in the first instance; or it passes right through the wall of the gut and comes to lie either in the vascular system or in the body-cavity.

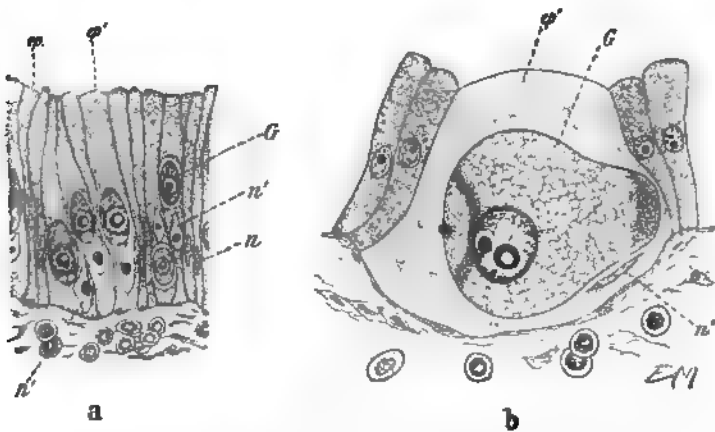


FIG. 32.—Intracellular stages of a gregarine, *Loukesteria ascidiae* in the intestinal epithelium of an ascidian. a, younger stages. b, older stage showing the hypertrophy of the epithelial cell induced by the parasite. ep, normal epithelial cell; ep', hypertrophied epithelial cell containing (g) a young gregarine; n, n, nuclei of normal and infected cells respectively. From Minchin, after Shoddekt, x750.

Gregarines in the latter position are commonly spoken of as "coelomic," without distinguishing between cases where the body-cavity is morphologically a true coelom, as in annelids, or a portion of the hæmocoel, as in arthropods. When special portions of the coelom are separated for a particular function, as in the case of the vesiculae seminales of the earthworm, the coelozoic stages may be found in these organs.

In the particular cavity, whichever it may be, that the trophozoite selects, it absorbs nutriment and gradually becomes full-grown and ripe for sporulation. Gregarines of enterozoic habitat may lie quite free in the lumen of the intestine, or may be attached to its epithelium by special organs of fixation (Figs. 33, 34). Those of coelomic habitat may be free in the body-cavity or its dependencies, or may be attached to its walls by tissue-growths forming cysts, never, however, by organs of fixation.

The body-form of gregarines is always definite, never amoeboid, and varies from a sphere or ovoid to an elongated worm-like shape. In those which attach themselves to the epithelium the fixation is effected by means of an organ termed an *epimerite*, derived from the rostrum of the sporozoite (Fig. 34). The epimerite is always cast off before sporulation, often at quite an early stage in the growth of the trophozoite. Hence

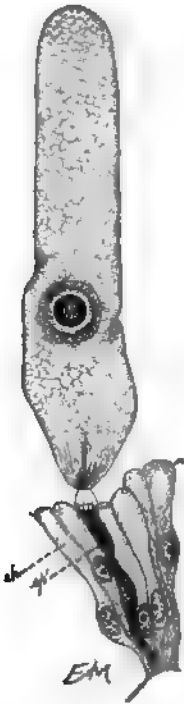


FIG. 33.—Young gregarine (*Lankesteria acclifera*), attached by a process to an epithelial cell (*ep.*), exfoliated by it. *ep.*, normal epithelial cells. From Minchin, after Siedlecki.  $\times 500$ .



FIG. 34.—A gregarine (*Pyralia ruberula* Haum.) attached by its epimerite to a detached epithelial cell. After Leger.

gregarines are often distinguished as cephalonts, with an epimerite, from sporonts, which are without it; but in many gregarines, especially those of early intracellular and later coelomic habitat, no epimerite is formed at any stage. By the presence or absence of this organ gregarines are classified into Cephalina and Acephalina. In many Cephalina the body behind the epimerite is further subdivided by a septum into an anterior portion termed a *protomerite* and a posterior portion termed a *dentomerite*. The biological significance of the septate condition is not clear.

The body is composed usually of granular endoplasm and hyaline

ectoplasm. The latter in its fullest development forms three layers, most externally a protective *epicyle*, internally to this the *sarcocyle*, and most internally a layer of contractile myonemes, termed the *myocyte*. Gregarines of colonic habitat, however, are more often motionless and have no myonemes. The ectoplasm then is a scarcely distinguishable clearer layer under the cuticle. The endoplasm contains the nucleus, always single, of large size and spherical form, and containing one or more large karyosomes.

The reproduction of gregarines consists in the vast majority of cases of sporogony alone, which has typically the following course (Fig. 35). Two

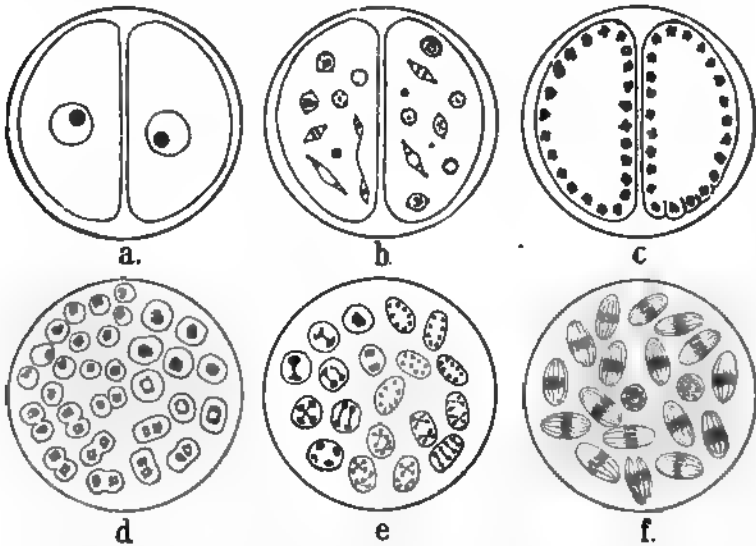


FIG. 35. Schematic figures of conjugation and spore-formation in gregarines. a, the two sporonts in a common cyst; b, various stages of nuclear division in the sporonts; c, commencing formation of gametes by a process of sporulation; d, union of gametes in pairs to form zygotes; e, a different stage of the process is seen in each quadrant of the figure; f, stages in the division of the nuclei of the zygotes or definitive sporoblasts. f, cyst with ripe spores (two seen in cross section), each containing eight sporozoites. From Minchin.

full-grown sporonts, perfectly similar one to the other in character, come together and become very intimately apposed, the adjacent surfaces being flattened by mutual contact, and the two bodies being sometimes closely entwined. Round the two individuals thus associated a cyst-wall is secreted (Fig. 35, a), after which they are quite independent of the host, and the subsequent development may go on in the open. In each individual a nuclear spindle is formed, but only from a very small part of the large nucleus of the trophozoite. The remainder of the original nucleus degenerates. The spindle gives rise to two daughter-nuclei, which divide again and again by mitosis, forming a very large number of small nuclei. These travel to the surface of the sporonts (Fig. 35, c), and each becomes budded off from the surface with a small amount of protoplasm

as a uninucleate cell, the primary sporoblast. The greater part of the protoplasm of each sporont is left over as a central mass of residual protoplasm, containing the remains of the trophozoite-nucleus. The primary sporoblasts become the gametes.

The gametes may be exactly alike, or may be differentiated into male and female, which may further be equal in bulk, or as in other gametes, the difference in size between male and female may be very marked (Fig. 36). In either case the male forms acquire a flagellum and a more elongated form of body and become motile, while the females are simply rounded cells

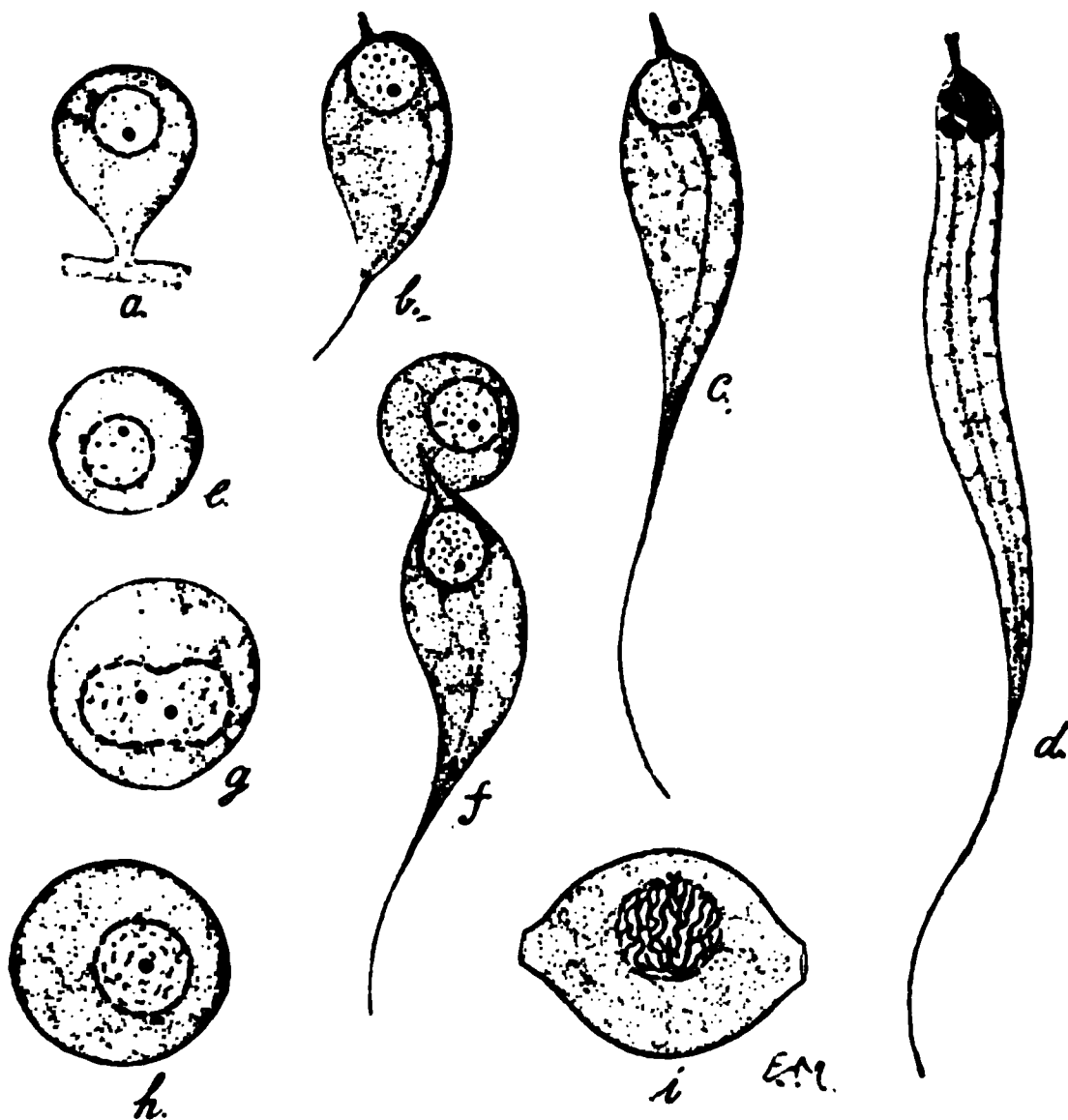


FIG. 36.—Development of the gametes and fertilisation in a gregarine (*Stylorhynchus longicollis* Stein). a, undifferentiated gamete still attached to the body of the parent gametocyte; b, c, d, evolution of the motile male gamete; e, mature female gamete; f, union of the gametes; g, nearly complete fusion of the gametes; h, the zygote, in i commencing to form the spore. From Minchin, after Leger, 1900.

without locomotor organs. When the gametes are thus differentiated, the sporonts from which they arise occupy distinct chambers separated by a partition in the cyst. Then in one chamber male gametes only, in the other female only are formed, shewing that the sporonts were of different sexes, although the differentiation was not apparent. When the gametes are ripe the active male forms break through the partition into the female chamber, and conjugate with the inert female gametes.

In the zygote both body and nucleus fuse completely to form the definitive sporoblast, round which appears a delicate membrane, very soon thickened to form the sporocyst or spore-envelope, and at the same time the body assumes a definite form, usually that of a barrel or spindle. Thus arises the characteristic gregarine spore, often termed by



older writers a pseudonavicella, on account of its resemblance to a diatom of the genus *Navicella* (Fig. 37). Each spore contains at first a simple mass of protoplasm with a single nucleus. The latter divides successively into

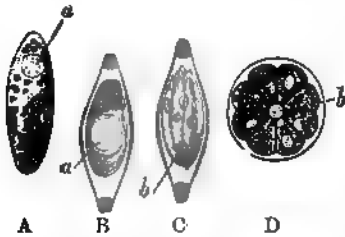


FIG. 37.—Development of the spore of a gregarine (*Monocystis*). A, oval sporoblast with single nucleus (a); B, formation of spore-membrane or sporocyst; C, ripe spore, containing eight sporozoites and residual protoplasm; D, diagrammatic cross-section of C. From Lankester, after Butschli.

two, four, and eight small nuclei, and then the protoplasm becomes split in a longitudinal direction into eight falciform bodies or sporozoites, arranged meridionally round a small quantity of residual protoplasm, the sporal residuum. Each sporozoite is a minute slender gregarinoid individual containing a compressed, refringent nucleus. When set free from the spore, an event which appears to occur normally in the digestive tract of a fresh host, the sporozoites perform active movements both of contractility and gliding locomotion, and by a combination of these movements they reach and penetrate into a host-cell. The anterior extremity is commonly differentiated as a rostrum, an organ of penetration and attachment, perhaps representing the flagellum of the Mastigophoran ancestor. A fresh trophic cycle is now started.

The gregarines are an extremely numerous order, and are differentiated into many families and genera. They may be classified as follows:—

Sub-order I.—*Schizogregarinae*.—This sub-order includes two genera, *Schizocystis* Léger and *Ophryocystis* Schneider, which have as a common feature reproduction by schizogony. In *Ophryocystis* the body was formerly wrongly described as amœboid, and hence this genus was placed in a special order, named Amœbosporida.

Sub-order II.—*Eugregarinae*. Schizogony very exceptional, and only occurs during the early cytozoic phase, if at all.

Tribe 1.—*Acephalina*.—Without epimerite and non-septate. Most of the members of this sub-order are “cœlomic” parasites, the youngest trophozoites being completely intracellular. The best-known genus is *Monocystis* Stein, of which at least two species occur almost constantly in the vesiculæ seminales of the earthworm.

Tribe 2.—*Cephalina*.—With an epimerite, usually also septate, sometimes, however, non-septate.

A great number of genera are referred to this subdivision. The type-genus *Gregarina* Dufour includes some very common species, among which may be noted *G. ovata* Duf. from the earwig; *G. blattarum* Siebold from the common cockroach; and *G. polymorpha* Hammerschmidt from the meal-worm; in each case intestinal parasites.

Mention must be made finally of the remarkable form described by Nussbaum as a gregarine under the name *Schaudinnella henlea*, parasitic in the intestine of an oligochaete worm *Henlea leptodera*. In this parasite the

trophozoites have an epimerite but are non-septate, and are distinguishable into male and female forms. Without encystation or association the trophozoites break up into gametes, the female forms into a few rounded ovum-like macrogametes, the male forms into numerous minute microgametes. Fertilisation takes place, and of the zygotes, some pass out of the intestine with the dejecta, and others penetrate into the epithelium of the gut and there sporulate, producing sporozoites which attach themselves to the epithelium and give rise to the adult trophozoites again, thus bringing about an auto-infection of the host. It is evident that if *Schaudinnella* be a gregarine at all, it differs from all other known representatives of the order in its method of reproduction, and it should perhaps be regarded rather as representing a distinct order of telosporidia intermediate between gregarines and coccidia.

2. *The Coccidiidea*.—Telosporidia typically of cytozoic habitat, parasites of epithelial cells, and always with distinct alternations of generations — namely, endogenous, non-sexual schizogony, and exogenous, sexual sporogony.

Only in a single case has a coccidian parasite of coelozoic habit been described. In all other known cases the parasite is intracellular during the entire trophic phase, living at the expense of a single epithelial cell, which it completely destroys. Within the host-cell the parasite grows into a rounded or spherical body, often with a marked resemblance, both in cytoplasm and nucleus, to an ovum. Hence the coccidia were sometimes described by older writers as “egg-like psorosperms.” When the trophic phase is at an end, the parasite abandons the withered host-cell and usually drops from the epithelium into the cavity lined by it, in order to sporulate, whether by the method of schizogony or sporogony. The epithelium most usually attacked by coccidian parasites is that of the gut or its dependencies, such as the liver; but other internal organs, such as the kidney, may be attacked. In no case is the epidermis or external body-epithelium known to be infected by true coccidia.

Speaking generally, coccidia occur frequently as parasites of those groups in which gregarines are rare or unknown, such as molluscs and vertebrates. On the other hand, they are found sparingly in those groups in which gregarines are common. In arthropods they are known in myriapods and a few insects, and in annelids they are rarely found. Quite recently a parasite apparently belonging to this order has been described attacking a gregarine. Many intracellular parasites, however, of one sort or another have been wrongly referred to this order, and it cannot be too strongly emphasised that an intracellular habitat is not the only characteristic of a coccidian parasite. In the vertebrata the coccidia have been found in all classes, and are alleged to occur in man, but no case of human coccidiosis has yet been satisfactorily investigated.<sup>1</sup>

The infection of coccidian parasites appears to start in all cases from the digestive tract of the host, as in the case of gregarines. Spores

<sup>1</sup> For an account of the cases known of coccidia occurring in man see article “Psorospermiosis”; also Brauu (8), Blanchard (3), and Lühe (46).

accidentally swallowed with the food are acted upon by the digestive juices, causing the contained sporozoites to be liberated. In the case of the common coccidian parasite of the rabbit, it has been shewn that the germination of the spores is brought about by the action of the pancreatic secretion, while the gastric juice has no effect upon them. Each sporozoite attacks and penetrates into an epithelial cell, usually of the intestine, but sometimes, as already stated, of some other internal organ, in which case the sporozoites must pass through the wall of the digestive tract and go through more or less extensive migrations in the body of the host. Within the host-cell the trophozoite may grow up either to become a *schizont*, multiplying by schizogony, or a *sporont*, multiplying by sporogony (Fig. 38).

The schizonts are generally formed at the earlier periods of the infection, when the parasites are still few, the nutriment consequently plentiful, and the host scarcely or not at all affected by them. A trophozoite destined to be a schizont grows rapidly, and when full grown its nucleus multiplies by repeated division to form several nuclei, round each of which the protoplasm segments to form a gymnospor, similar in the main to a sporozoite, but on account of its different origin termed a *merozoite* (Fig. 38, II-IV). The merozoites are commonly, though not invariably, arranged like the staves of a barrel round a central mass of residual protoplasm, the whole being a so-called "corps en barillet," which may be enclosed in a *cytost*, that is to say, in the remains of the host-cell, but not in any secreted protective cyst.

The merozoites soon separate off and wander away as tiny gregarinoid bodies, each of which attacks an epithelial cell, as did the sporozoites in the first instance. Thus arises another generation of trophozoites, which may in their turn grow up to become either schizonts or sporonts. Usually, however, several generations of schizogony first run their course, whereby the host becomes overrun by the parasite and may be greatly weakened, before sporonts appear.

In proportion as the effects of the continually increasing numbers of the parasites begin to make themselves felt by the host, so the host begins to react on the parasites, either by scarcity of nutrition, owing to the ravages of the parasite in the tissues, or by defensive processes of one kind or another. As a result, the process of multiplication by sporogony begins to supplement that of schizogony to an ever-increasing degree, until finally only resistant cysts and spores are found, which pass out of the host. The body is thus gradually purged of the parasites, with consequent healing and recovery from their effects. The host is not, however, thereby rendered immune to a fresh infection (Schaudinn). In reproduction by sporogony the process is initiated by merozoites developing into sporonts instead of into schizonts. The sporonts are trophozoites, which grow much more slowly than the schizonts, and which are differentiated into two kinds, distinguishable by the characters of their cytoplasm and nucleus both from one another and from the indifferent schizonts. In one class of sporont the cytoplasm is relatively

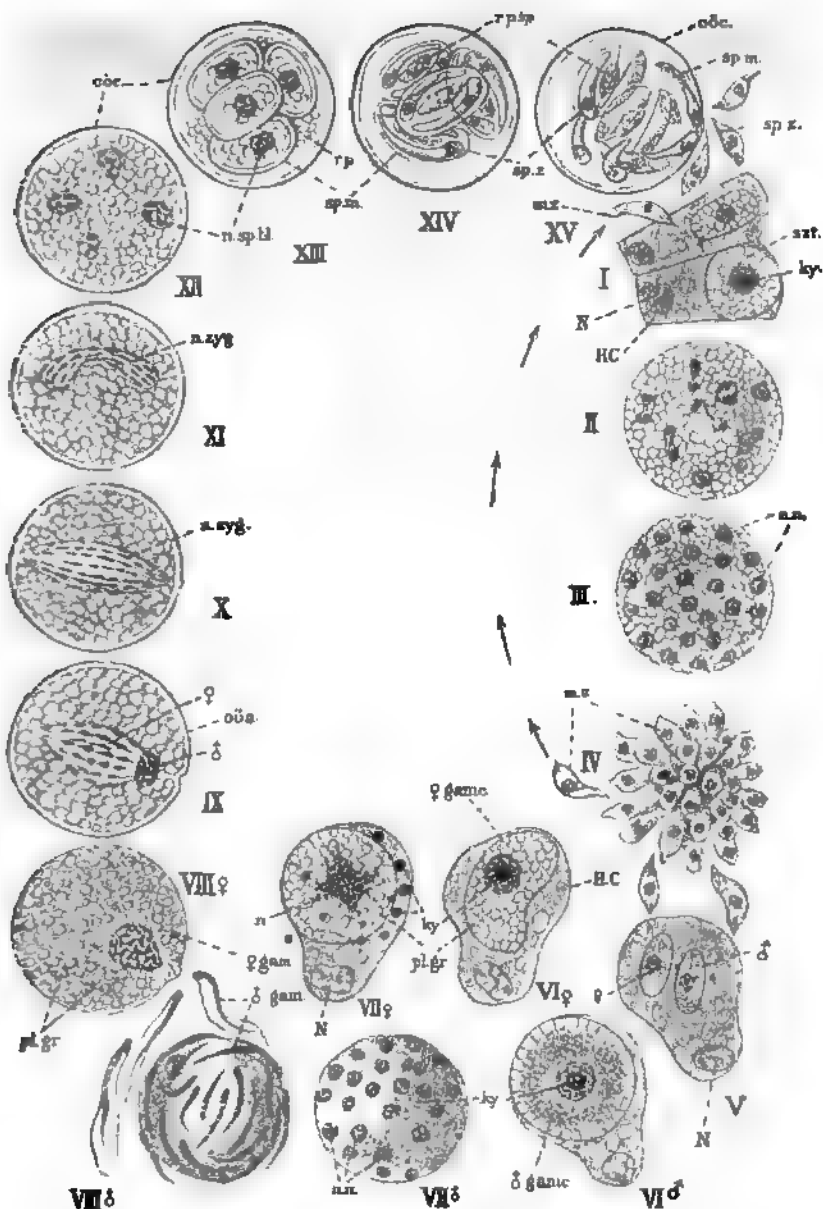


FIG. 38. — Diagram of the life-cycle of *Coccidium schubergi* Schaud. in the centipede *Lithobius forficatus*. I-IV, the endogenous non-sexual cycle, or schizogony; V-VIII, the development of the gametes, along two lines, ♂ and ♀; IX, X, the zygote; XI-XV, sporogony. I, two epithelial cells, showing the penetration by a merozoite (mz) and the growth of the latter into a schizont (sz), with a conspicuous karyosome (ky); H.C., host-cell; N, its nucleus. II and III, full-grown schizonts showing division of the nucleus; a daughter nuclei, each with a karyosome. IV, "rosette" of merozoites (mz). V, cell containing two young gametocytes, of different sexes. VI ♂ and VI ♀, full-grown gametocytes (gamc), the female characteristically bean-shaped and full of granules of reserve material (pl.gr). VII ♂, division of the nucleus in the male gametocyte, the karyosome (ky) being left over at the centre of the protoplasm. VII ♀, maturation of the female gametocyte by expulsion of the karyosome (ky). VIII ♂ and VIII ♀, mature male gametes (♂ gam) leaving the body of the gametocyte and passing over to the mature female gamete (♀ gam). IX, zygote with male and female pronuclei (♂ and ♀) and oocyst at the surface (ooc). X, zygote with fertilisation spindle (s.sp). XI, XII, division of synkaryon to form four sporoblast nuclei (a.sp.b). XIV, ripe cyst containing four spores, each containing two sporozoites (sp.z) and a sporal residuum (r.p.sp) and imbedded in residual protoplasm (r.p); sp.m., sporocyst. XV, escape of sporozoites from the cyst. From Munchin, after Schaudtton.

clear and free from coarse granulations, and the nucleus is large; these are the sporonts of male character or microgametocytes (Fig. 38, VI ♂). In the other type of sporont the cytoplasm is opaque, and loaded with coarse granules or spherules of plastin, and the nucleus is relatively small; these are sporonts of female character, macrogametocytes (Fig. 38, VI ♀). In some cases the female sporonts may be very much larger than the males, and early association, as in gregarines, may take place between them, a well-known example of which is *Adelea orata*, parasite of *Lithobius forficatus* (Fig. 40). In some coccidia the schizonts are

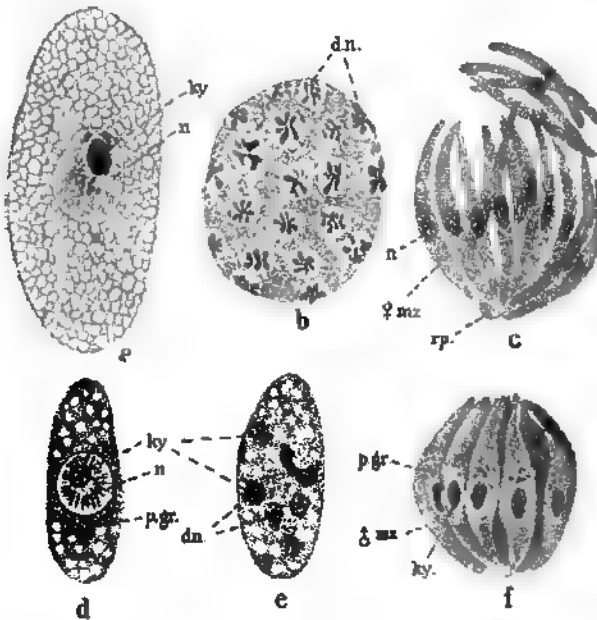


FIG. 39.—Schizogony of *Adelea orata* Schneider, parasitic in the centipede *Lithobius forficatus*. a-c female line, d-f, male line. n, nucleus; ky, karyosome; d u, daughter-nuclei; ♀ mz, ♂ mz, female or male merozoites, rp, residual protoplasm; p.gr, pigment granules. From Muchin, after Nisollecki.

sexually differentiated from the first as well as the sporonts, and there are no schizonts of indifferent character. There is then a series of schizogonous generations of male or female forms, of which the end term in each case is the gametocyte which produces the gametes (Fig. 39).

The microgametocytes produce microgametes by a process of sporulation. Schaudinn describes the process in *Coccidium schubergi* as commencing by the large, centrally placed nucleus giving off very numerous chromidia, minute granules of chromatin, into the cytoplasm. The chromidia travel to the surface of the body and become concentrated into patches, each such patch becoming further condensed into a nucleus consisting ultimately of closely packed, refringent chromatin (Fig 38,

VII  $\delta$ ). Each nucleus thus formed becomes elongated in form, and gradually separates off from the parent body to form a microgamete, which consists mainly of chromatin with a scarcely perceptible envelope of protoplasm (Fig. 38, VIII  $\delta$ ). In most cases the microgametes have two flagella, usually differing in length and movements; they either arise both together from the end anterior in movement, or one arises

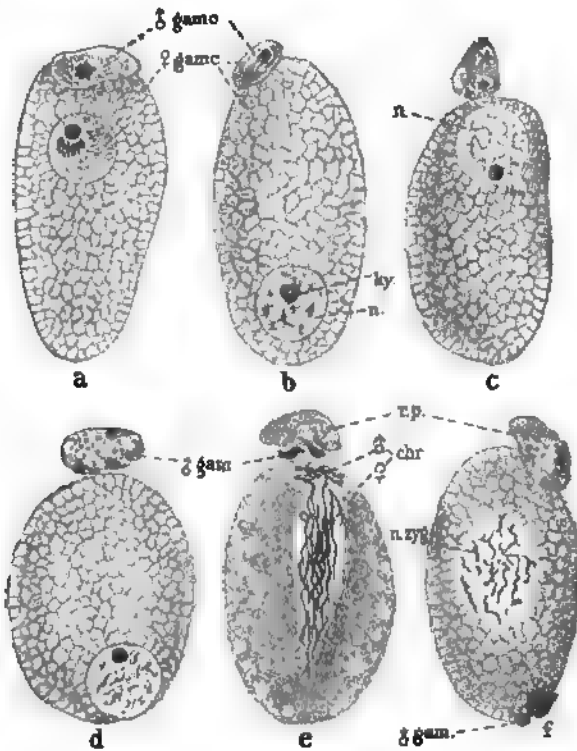


FIG. 40.—Conjugation of *Adelea ovata* Schneider. a, association of a male and female gametocyte ( $\delta$  gamc,  $\gamma$  gamc); b and c, division of the nucleus of the male gametocyte into four, n, nucleus of the female gametocyte; ky, its karyosome; d, formation of four male gametes ( $\delta$  gam); e, zygote with male and female pronuclei ( $\delta$ ,  $\gamma$  chr), attached to which are three superfluous male gametes and the residual protoplasm (r.p.) of the male gametocyte; f, zygote with synkaryon (n.zyg) and with residual male gametes, etc., as in last. From Minchin, after Siedlecki.

from the anterior, the other from the posterior end, so that the arrangement of the flagella is distinctly of the heteromastigote type. In some cases no flagella are present, and the microgamete progresses by serpentine movements of the whole body. Usually very numerous microgametes are produced from each parent gametocyte, but in cases where early association of the sporont occurs, as in *Adelea ovata* mentioned above, the number of microgametes may be reduced to four only. After formation of the microgametes, the body of the microgame-

toocyte or sporont, scarcely reduced in size, gradually dies off and disintegrates, together with the remains of the large sporont nucleus.

In female sporonts or macrogametocytes the process of sporulation to produce gametes is in abeyance, and each macrogametocyte simply becomes a macrogamete after going through a process of maturation by elimination of a portion of the nuclear substance. The manner in which this maturation is effected appears to vary considerably in the group. In *Coccidium schubergi* Schaudinn describes it as taking place simply by the ejection of the karyosome, first from the nucleus, then from the body of the sporont (Fig. 38, VII ♀). In *Cyclospora caryolytica* of the mole the same author describes two divisions of the nucleus forming three nuclei, two of which degenerate, while the third becomes the pronucleus.

A single microgamete, as a rule, penetrates into the cytoplasm of the macrogamete, which forms a "cone of reception" at the point of entry (Fig. 38, VIII ♀). In *Cyclospora caryolytica*, however, several microgametes may enter, but in all cases only one effects the actual fertilisation, that is to say, the fusion between the two pronuclei of the microgamete and macrogamete respectively. The chromatic substances of the two pronuclei become intermingled by the formation of a so-called fertilisation-spindle, formed as follows:—The female pronucleus first assumes the form of a spindle stretching across the whole body of the zygote, in which fine grains of chromatin are arranged in meridional rows, running from one pole of the spindle to the other. The male pronucleus then breaks up also into fine grains of chromatin, which become spread over the spindle. When this process is complete the spindle gradually contracts into a rounded form, thus producing a synkaryon in which the male and female chromatin is intimately blended (Fig. 38, IX, X).

In most cases the macrogamete previous to fertilisation has the surface of the body quite naked and unprotected by any envelope of any kind. Then the microgamete enters at any point, and immediately after its entry has been effected, a clear membrane, at first thin but gradually increasing in thickness, makes its appearance over the surface of the zygote and prevents the entry of further gametes. This membrane becomes a tough resistant cyst, termed an *oöcyst*, in which spore-formation takes its further course (Fig. 38, IX). In some cases, however, especially among the coccidia of vertebrates, the oöcyst is formed before fertilisation, and then has a minute pore or micropyle through which the microgamete enters. The pore is protected by a plug of protoplasm, which, after entry of the microgamete, closes up the micropyle completely. The presence of an oöcyst at once distinguishes sporogony from schizogony, no cysts being secreted in the latter mode of reproduction. As soon as the fertilisation is complete the synkaryon begins to divide by the direct method, *i.e.* without mitosis, to form the nuclei of the sporoblasts. The process of spore-formation varies considerably in details, as is evident from the classification in current use given below, which is founded on the variations on the spore-formation. The following points, however, may be stated generally.

Within the oöcyst the zygote becomes divided into a number of uninuclear masses, the sporoblasts, arranged round a central protoplasmic residuum. Each sporoblast may now simply become converted into a gymnospor or sporozoite, or may surround itself by a tough membrane or sporocyst to form a resistant spore. Within the sporocyst, when formed, the protoplasm may become a single sporozoite, or may become divided up to form two or more sporozoites, altogether with a certain amount of residual protoplasm. Great variation is seen in the spores of coccidia with regard to the number of sporozoites they contain. Hence they are characterised in technical language as monozoic with one sporozoite, dizoic with two, trizoic with three, tetrazoic with four, and polyzoic with many sporozoites. The octozoic condition, with eight sporozoites, which is the rule with few exceptions in gregarines, is rarely found in coccidia.

The order Coccidiidea is commonly classified into four subdivisions or families based on the number of resistant spores, if any, formed in the oöcyst.<sup>1</sup>

Family 1.—*Asporocystidae*.—No sporocysts, only naked sporozoites, formed in the cyst. A single genus *Legerella* Mesnil (*Eimeria* A. Schn.).

Family 2.—*Disporocystidae*.—The oöcyst contains two spores. In *Cyclospora* A. Schn. the spores are dizoic; *C. caryolytica* Schaud. is an intranuclear parasite of the intestinal epithelium of the mole. In *Diplospora* Labbé the spores are tetrazoic; several species are known, parasitic in reptiles and birds.

Family 3.—*Tetrasporocystidae*.—The oöcyst contains four spores. The most important genus is *Coccidium* Leuck. (perhaps more correctly named *Eimeria*), parasitic on vertebrates of all orders.

Family 4.—*Polysporocystidae*.—The oöcyst contains numerous spores. Many genera are referred to this family, nearly all of which are parasites of invertebrates. The best-known genera are *Adelea* A. Schn., dizoic, and *Klossia* A. Schn., tetrazoic.

3. *Hæmosporidia*.—Telosporidia with alternation of generations corresponding with an alternation of hosts; parasitic, during the non-sexual schizogonous cycle, in the blood of a vertebrate, and during the sexual, sporogonous cycle, in the gut of an invertebrate host.

The hæmosporidia as blood-parasites of man and various vertebrates are of great importance from the medical point of view. It may be doubted, however, whether the order should be regarded as a natural and homogeneous group, like the gregarines or coccidia. The various types referred to this order do not appear to have much in common, beyond the fact that they are parasites of the blood of vertebrates, of intracorpuseular occurrence during the whole or part of their endogenous cycle, and that their transmission from one vertebrate host to another is effected by some invertebrate animal of blood-sucking habit, in which the sexual cycle of the parasite takes place. At least four distinct generic

<sup>1</sup> A more modern and perhaps less artificial classification of the coccidia is given by Luhe (46).



types are referred to this order, the characteristics of which are best described separately. These are the genera *Plasmodium* (*Hæmamaeba*), *Hæmogregarina*, *Piroplasma*, and *Halteridium*.

(1) *Plasmodium* Marchiafava and Celli (including *Hæmamaeba* Grassi and Feletti; *Laverania* Grassi and Feletti; *Hæmomenas* Ross; *Hæmoproteus* Kruse; *Proteosoma* Labbé; *Achromaticus* Dionisi; *Polychromophilus* Dionisi; and *Hæmocystidium* Castellani and Willey) comprises the various malarial parasites of mammals and birds, the agent of transmission being in all known cases a gnat or mosquito of the dipterous family *Culicidæ*. The trophozoite is always of amœboid form, and is intracorpuseular during the whole trophic phase. A characteristic feature of all malarial parasites is the production of an excreted pigment termed *melanin*, derived from the hæmoglobin of the blood.

The life-cycle of the **malarial parasites** is of the same type as that of the coccidia, allowing for differences due to the fact that in the former the schizogony and sporogony are in different hosts. The malarial parasites of man are the best known and most thoroughly studied in all stages of their life-history, and the following account applies to them more especially.

Opinions are not unanimous on the question of the number of species of the malarial parasites found in man. Laveran, their discoverer, regards them all as one species, with a number of varieties. Most authorities, however, are agreed in recognising three species; these are—(1) *Plasmodium vivax* (Gr. et Fel.), the tertian parasite; (2) *P. malariae* (Lav.), the quartan parasite; (3) *P. immaculatum* (Gr. et Fel.), the parasite of pernicious or tropical malaria.<sup>1</sup> Other species of the genus are *P. kochi* (Lav.), from monkeys; *P. præcox* (Gr. et Fel.), synonyms *Hæmoproteus danilewskyi* Kruse, *Proteosoma grassii* Labbé, from various birds (Fig. 45); and several species, not as yet adequately characterised, from bats and other mammals or birds. Three species occurring in reptiles have also been referred to this genus, so that malarial parasites appear not to be confined exclusively to warm-blooded animals.

The three human malarial parasites are distinguished by morphological points, which will be mentioned in describing the various stages of the life-cycle, and also by their effects on the host. They produce fevers which recur at regular intervals, each access of fever coinciding with the endogenous sporulation of the parasite, at which period vast numbers of merozoites, set free in the blood, are attacking fresh corpuscles. In the quartan parasite a schizogonous generation takes seventy-two hours, and the fever recurs every three days. In the tertian parasite each generation takes forty-eight hours, and the attacks recur every other day. In pernicious malaria the sporulation takes place irregularly, and the fever is irregular or continuous. Pernicious malaria is, moreover, at

<sup>1</sup> The nomenclature of the malarial parasites is extremely confused, and no two authorities use the same names. The terminology followed here is that given by Schaudinn (73). The parasite of pernicious malaria is commonly known as *Laverania malariae* (Gr. et Fel.). According to Blanchard, the parasite of pernicious malaria should be named *Plasmodium falciparum* (see article "Malaria"). *Quot auctores tot nomina!*

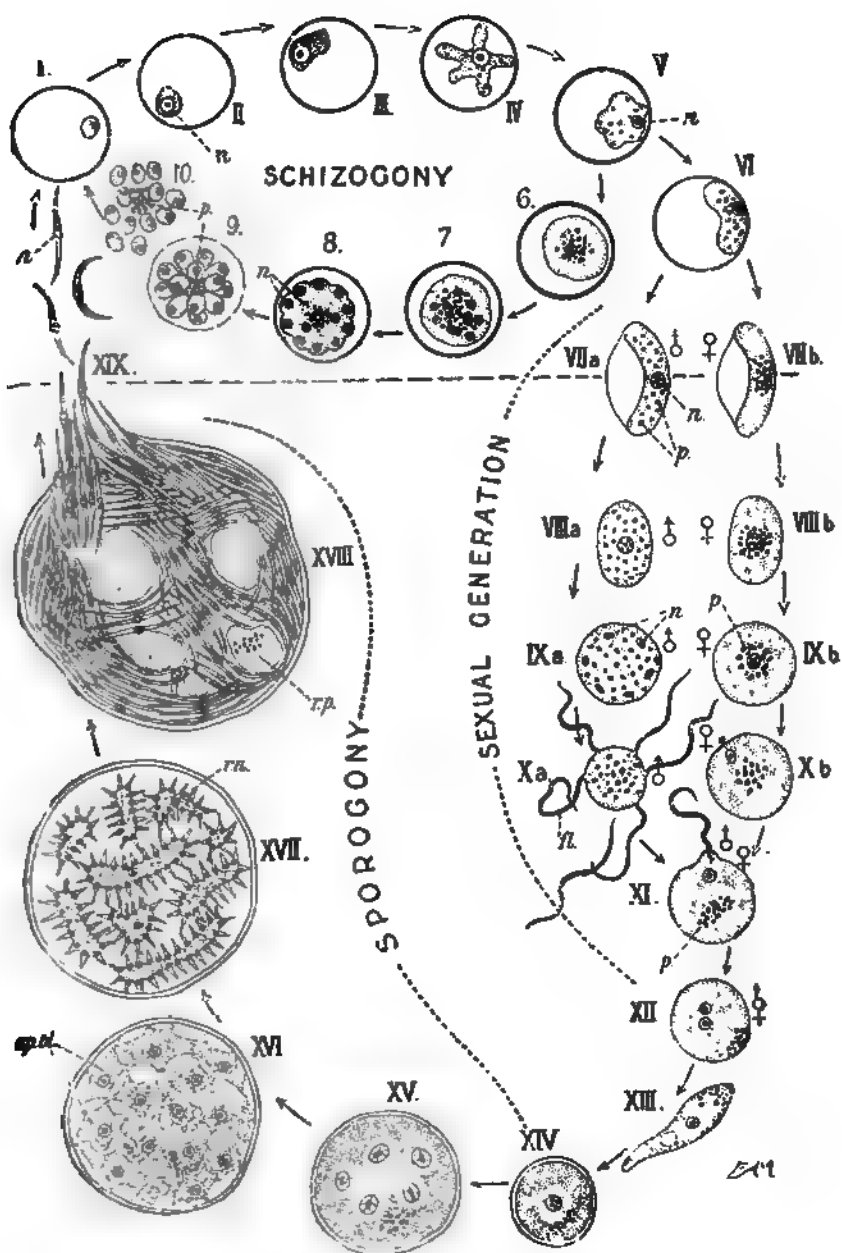


FIG. 41. — Diagram (not strictly accurate in all details) of the complete life-cycle of the parasite of human pernicious malaria, *Plasmodium vivax* (Gr. et Pel.). The stages above the dotted line are found in human blood, those below the line in the mosquito. I-V and 6-10 show the schizogony; VI-XII, the sexual generation, which at VII splits into two lines, (a) male and (b) female, which are united again by conjugation, XI and XII; XIII, motile zygote, vermicle or ookinete, XIV-XIX, sporogony; n, nucleus; p, melanin-pigment; r.p., male gametes, so-called flagella; sp., sporoblast nuclei; r.n., residual nuclei; r.p., residual protoplasm. From Minchin.

once distinguished from the other two by the crescent-shape of the gametocytes. The different types of parasite also produce characteristic effects upon the blood-corpuscles attacked by them. The quartan parasites cause the corpuscle to diminish in size, while retaining its normal colour. Corpuscles attacked by the tertian parasite, on the contrary, increase considerably in size, and become paler. The effect produced by the pernicious parasite is not so constant, the corpuscle becoming enlarged or diminished, with a lessened or a heightened tint.

The endogenous cycle, or schizogony (Fig. 42), commences, in the case of a new infection, with sporozoites introduced into the blood by the proboscis of an infected mosquito. The first sporozoites thus inoculated probably grow up in all cases to become schizonts. Each sporozoite penetrates into a blood-corpuscle and becomes an amoeboid trophozoite, which grows

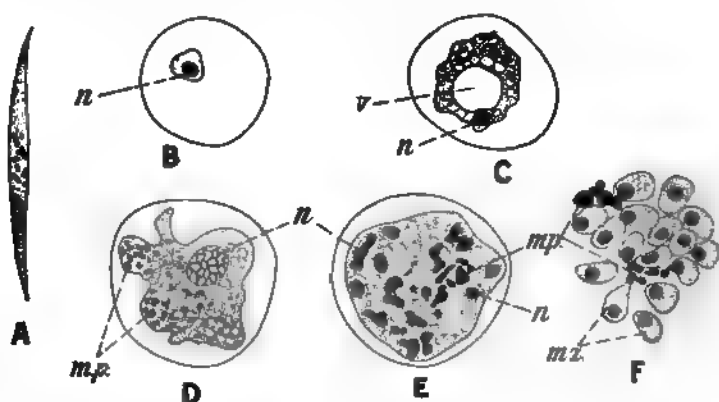


FIG. 42.—Schizogony cycle of *Plasmodium vivax* (Gr. et Fel.). A, sporozoite; B, youngest intra-corpuscular stage; C, signet-ring stage; D, nearly full-grown schizont; E, schizont with nucleus dividing up; F, "rosette" of merozoites with residual pigment, etc.; n, nucleus; v, vacuole; m.p., melanin-pigment; mz, merozoites. After Schaudinn.

rapidly without leaving the corpuscle. The degree to which the parasites are amoeboid varies in different species, and is most marked in the tertian parasite. Characteristic of young trophozoites destined to become schizonts is the peculiar "ring-form," caused, according to Schaudinn, by the formation near the nucleus of a vacuole, which, increasing in size, gives the whole parasite the form and appearance of a signet-ring. Schaudinn is of opinion that the ring-form serves to increase the body-surface of the parasite, and favours rapid absorption of nutriment and growth on the part of the trophozoite. As the parasite grows the vacuole disappears, and the characteristic grains of melanin-pigment appear.

In the fully formed schizont the body becomes compact and rounded off, ceasing to be amoeboid, and the nucleus begins to divide up into a number of small masses, usually nine to twelve in the quartan parasite, twelve to twenty four in the tertian parasite, and a variable number in the pernicious parasite. The protoplasm then becomes segmented up

round each of the nuclei to form a corresponding number of merozoites, leaving a small amount of residual protoplasm containing the melanin-pigment. The merozoites are small rounded bodies grouped more or less regularly round the residual protoplasm, the whole forming a so-called rosette-stage. While the sporulation is proceeding the corpuscle gradually disintegrates, and when the process is complete the rosette is free in the blood-plasma. The merozoites when fully developed wander off, abandoning the residual protoplasm and melanin-pigment, and each merozoite, if it escape the leucocytes, penetrates a blood-corpuscle and becomes a trophozoite of a second generation. In the tertian and quartan parasites the sporulation takes place in the peripheral blood-stream, but in pernicious malaria sporulating forms are to be sought chiefly in the internal organs, especially the liver, spleen, and bone-marrow.

When the parasites are first introduced into the blood their numbers are relatively small, and hence for a certain period they produce no appreciable effect upon the host. This is the so-called incubation-period, varying in different species between six and twelve days. It is probable that during the incubation-period schizogony only goes on, the sporozoites or merozoites all developing into schizonts, which produce merozoites again. As this method of reproduction causes the numbers of the parasite to increase by geometrical progression, they soon begin to bring about a reaction on the part of the host, which is manifested in the symptoms of fever. The reaction of the host upon the parasite is, according to Schaudinn, the stimulus which determines in the latter the production of sexually differentiated sporonts, destined for exogenous reproduction.

The growth of a merozoite into a sporont is much slower than in the case where it grows into a schizont, and is characterised by the absence of a ring-stage in the young trophozoites (Schaudinn). The sporonts are always of two kinds, representing male and female gametocytes, which can be distinguished both from one another and from the schizonts. It may be said generally that in the male sporonts the nucleus is more developed, and the cytoplasm is free from granulations of reserve material, and hence stains lightly, while in the females the reverse is the case, the nucleus being relatively small and the cytoplasm full of granulations, causing it to stain deeply.

In pernicious malaria the sporonts are at once distinguished from the schizonts by their form, like that of a sausage, and are hence known as "crescents." In the male crescents the pigment-granules are apt to be more evenly scattered, while in the female forms the pigment tends to be more aggregated round the nucleus (Fig. 41, VII).

In the tertian and quartan parasites the sporonts are not characterised by any special body-form, but can still be distinguished by their characters. Thus in the tertian parasite, which has been most accurately studied, the full-grown schizonts are about  $10\mu$  in diameter, with a nucleus situated at the periphery of the body. The female sporonts are larger,  $12-16\mu$  in breadth; their dense cytoplasm stains deeply, and their grains of

melanin-pigment are two or three times as large, and about twice as numerous as those of the schizont, but, as in the latter, the nucleus is situated eccentrically. The male sporonts are distinguished in all stages

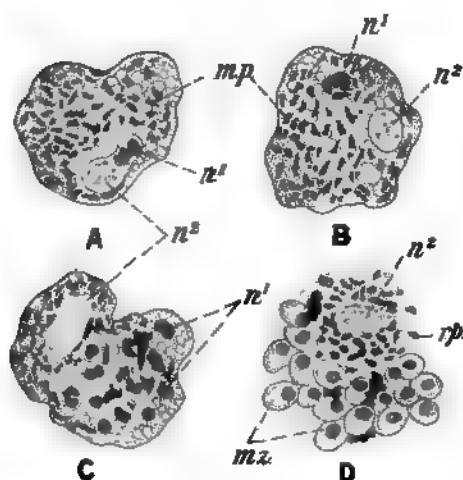


FIG. 43.—Parthenogenesis of *Plasmodium vivax*. A, a female gametocyte of which the nucleus is dividing into a darker ( $n^1$ ) and a lighter portion ( $n^2$ ); B, the separation of the two parts of the nucleus is complete; C, the darker nucleus has divided into a number of portions; D, a number of merozoites are formed from the darker nuclei; the lighter nuclei are abandoned in the residual protoplasm (r.p.) containing the melanin-pigment. After Schaudinn.

by their large nucleus placed at or near the centre of the body; the melanin-pigment is as well developed as in the females, but the protoplasmic portion of the body is feebly developed as compared with the other two forms, and is less dense, and stains a much lighter tint. The sporonts are less amoeboid than the schizonts in early stages of growth, the male sporonts least of all so. The early stages of the sporonts or gametocytes are to be sought in the internal organs, especially the spleen and bone-marrow, but when full grown they circulate in the peripheral blood, whence in the natural course of events they are taken up by a mosquito,

in order to undergo in its digestive tract a process of development, of which they are not capable in the blood and at the temperature of the warm-blooded host. If not taken up by a mosquito, the male sporonts appear simply to die off, without undergoing further development, but the female sporonts are more resistant, on account of the reserve material stored up in their abundant cytoplasm, and according to Schaudinn, they are capable of outliving all other forms of the parasite in the human body, and then multiplying by parthenogenesis to produce fresh schizogonous generations (Fig. 43), which cause the relapses so often observed in these fevers. It has been shown above in the case of *Coccidium* that the host may be purged of the parasites, because they all develop into sporonts which form resistant cysts and pass out of the body. If a similar process of development be supposed to occur in a malarial parasite, the disappearance of all schizogonous stages from the blood would doubtless bring about an alleviation of the symptoms of disease and an apparent recovery from the fever; but the sporonts, not being able to escape by natural channels from the body, like coccidian cysts in the digestive tract, would remain in the blood, and after a time only the resistant female forms would be left. A similar state of things would result if we suppose the more delicate

schizonts and male sporonts to be killed off by the action of some drug administered, such as quinine, which the more resistant female sporonts may be able to withstand, possibly by passing into some protected or resting form, still to be discovered, in the internal organs of the body; or perhaps by a greater hardness of constitution characteristic generally of forms destined for exogenous reproduction, that is to say, for adapting themselves to entirely changed conditions.

The stimulus to the renewed activity of the parasite which brings about a relapse is perhaps supplied by some external cause, such as a chill or shock to the system, which lowers the resistance of the host. The parthenogenesis of the female sporonts (Fig. 43), as described by Schaudinn, is essentially similar to the process already described above in trypanosomes, and consists in the gametocyte being set back into the indifferent or schizont form, after which it sporulates in the usual endogenous manner. The nucleus of the gametocyte divides into two parts; one is rich in chromatin and stains deeply, while the other is pale and stains feebly. The body becomes partially constricted into two parts, one consisting of denser protoplasm, with most of the pigment and the pale nucleus; this portion of the body with its contents is ultimately abandoned as residual protoplasm; the other portion has lighter protoplasm and less pigment, and contains the darker nucleus; this portion proceeds to sporulate as in the schizogony, and produces a number of merozoites, which attack red blood-corpuscles, and give rise to a fresh endogenous cycle, and consequently a relapse of the fever.

To return now to the gametocytes. When taken up by the mosquito, the action of the digestive juices of the new host has the effect of causing all stages of the parasite to be digested along with the blood, except the ripe gametocytes, but has no effect upon the latter other than that of setting them free from the last remains of the blood-corpuscles, whereupon the crescents of the pernicious parasite assume the spherical form already possessed by the gametocytes of the tertian and quartan parasites. Formation of gametes commences immediately, the chief stimulus to this development being apparently the lowering of temperature, since the whole process can be observed under the microscope in blood drawn fresh from the body and studied *in vitro*.

In the male gametocyte the nucleus gives off chromidia, which travel to the surface of the body, leaving a karyosome or remains of the sporont nucleus at the centre (Fig. 44, D, E). With great rapidity motile threads, four to six in number, are shot out from the surface of the body. These threads are commonly termed flagella, but are in reality microgametes, and contain all the peripheral chromatin given off from the nucleus of the gametocyte. The microgametes lash wildly about until they become detached from the body of the gametocyte, which perishes as residual protoplasm together with the contained karyosome. Each microgamete is a slender body which progresses by serpentine movements, and consists chiefly of chromatin. It is strictly comparable to a coccidian microgamete of the type in which flagella are lacking, and also may be com-

pared structurally to a form of spirochaete without an undulating membrane, for example *Treponema* (see p. 47). The formation of the microgametes is a phenomenon which can be observed very easily and has long been known, though only comparatively recently explained. Since this stage was mistaken by earlier observers for an independent flagellate organism, it is sometimes known as the *Polymitus* stage, and the

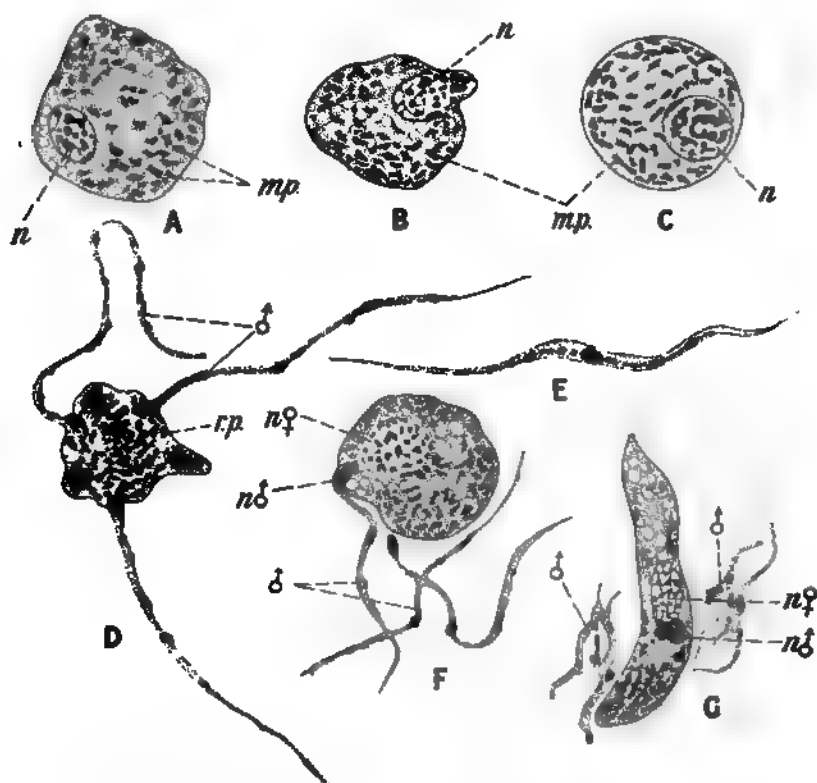


FIG. 44.—Gamete-formation and fertilisation in *Plasmodium vivax*. A, full-grown female gametocyte; B, the same extruding a portion of the nucleus as a polar body; C, full-grown male gametocyte; D, formation of male gametes, three of which have been extruded, and three more are about to be; E, a male gamete; F, fertilisation of a female by one of three male gametes; G, an ookinete, surrounded by degenerated remains of superfluous male gametes; ♂, male gamete, n♂, n♀, nuclei of male and female gametes; other letters as before. After Schaudinn.

whole process is commonly called flagellation, a term quite inexact and inadmissible from the zoological point of view.

In the female gametocyte the process of sporulation is in abeyance, and, as in coccidia, each gametocyte becomes a macrogamete after elimination of a portion of the nuclear substance (Fig. 44, A-C).

The microgametes formed as described above seek out the macrogametes, penetrate into them, and fertilise them (Fig. 44, E, F). The

chromatin contained in the microgamete forms a pronucleus which fuses with the female pronucleus of the macrogamete with the formation of a fertilisation-spindle, as in coccidia. The zygote does not, however, secrete a protecting envelope or cyst, but becomes elongated in form and develops into a motile gregarinoid individual termed a vermicule or *oökinete* (Fig. 44, G). This motile stage represents the oöcyst-stage in the life-cycle of the coccidia, and is practically the only point in which the life-cycles of the malarial parasites and the coccidia differ to the extent of requiring the use of a distinct terminology. The vermicule moves forwards with the characteristic gliding movements described above (p. 58). Its anterior extremity is narrow, almost pointed, and rather drawn out; the nucleus (synkaryon) is near or slightly behind the middle of the body; and the grains of melanin-pigment are lumped at the hinder end of the body, whence they may be extruded with a small quantity of protoplasm, or may be retained till sporulation and then abandoned with the residual protoplasm. By its own activity the vermicule pushes its way through the epithelial lining of the mosquito's stomach and comes to rest immediately below the epithelium. In this situation it becomes spherical in form (Fig. 41, XIV) and a delicate membrane is formed enveloping it, perhaps secreted by the host, and in any case not a tough, impervious envelope like the oöcyst of coccidia, since the parasite commences to absorb nourishment from the host and to grow until it bulges out the stomach-wall towards the body-cavity. Within the cyst the nucleus (synkaryon) multiplies by division as the parasite increases in size, and round the daughter-nuclei thus formed the protoplasm becomes concentrated to form a number of sporoblasts imperfectly separated from one another (Fig. 41, XV, XVI). In each sporoblast the nucleus, at first single, divides repeatedly to form various small nuclei, which travel to the surface of the sporoblast, and grow out each in a slender protoplasmic projection to form a gymnospor or sporozoite (Fig. 41, XVII). In this way the cyst becomes filled with a crowd of sporozoites, varying in number from some hundreds to over ten thousand, together with a certain amount of residual protoplasm derived from the sporoblasts or from the vermicule (Fig. 41, XVIII). When the contents are ripe the cysts become ruptured into the body-cavity (hæmocœle) of the mosquito. The sporozoites thus set free are minute spindle-shaped bodies, each actively motile. They are carried along in the blood fluid, but ultimately pass into the salivary glands, and penetrate the secreting cells, which may be filled by them. When the mosquito next takes a feed of blood, the sporozoites in the salivary gland pass down the proboscis into the blood of the vertebrate host, in which, if of the kind suited for the development of the parasite, they start a fresh endogenous cycle of generations.

The entire exogenous cycle in the body of the mosquito lasts some ten or twelve days, so that the mosquito is not infectious until its third or fourth meal after that at which it acquired the infection. Mention must be made of the so-called "black spores" frequently seen in infected mosquitos, apparently representing degenerated cysts of the parasite in



which a mass of pigment has been produced by the abnormal activity of the protoplasm.

The human malarial parasite is transmitted by a gnat of the genus *Anopheles*; that of birds (*Plasmodium præcox*) by a gnat of the genus *Culex*. The intermediary for the parasites of monkeys (*P. kochi*) is as yet unknown, and the same applies to the similar parasites described in bats.

(2) *Hæmogregarina* Danilewsky (including *Danilewskyia* Labbé, *Karyolysus* Labbé, *Drepanidium* Lankester, *Lankesterella* Labbé, *Dactylosoma* Labbé) comprises a number of forms parasitic chiefly in cold-blooded vertebrates. The body of the parasite is not amœboid, but of definite form, which is typically that of a minute vermicule or gregarinoid individual, actively motile when set free from the corpuscle. Its cytoplasm does not contain melanin-pigment at any stage. Endogenous reproduction is usually by schizogony, sometimes simply by fission.

Various generic subdivisions of the Hæmogregarines have been

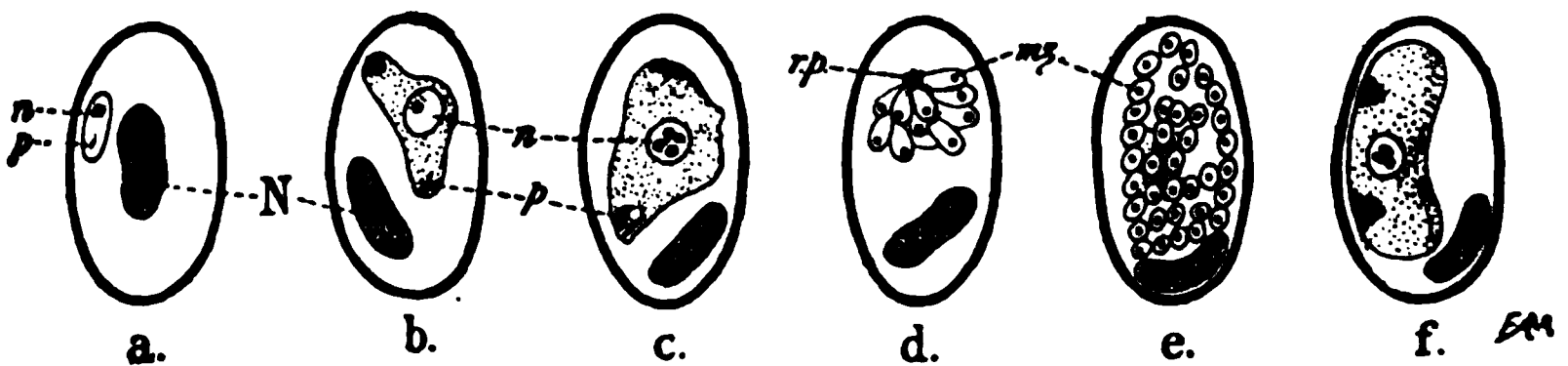


FIG. 45.—*Plasmodium præcox* in the blood-corpuscles of birds. a, young; b and c, older trophozoites; d and e, sporulation, shewing variations in numbers of merozoites formed; f, gametocyte; N, nucleus of blood-corpuscle; n, nucleus of parasite; p, pigment; mz, merozoites; r.p., residual protoplasm. After Labbé,  $\times 1200$ .

proposed, based on the relative proportions of the parasite and the blood-corpuscle it attacks. Thus, in *Lankesterella* (*Drepanidium*) the parasites are minute, not more than three-fourths the length of the corpuscle (Fig. 46); in *Karyolysus* the parasite does not exceed the blood-corpuscle in length, and the known species of this genus, of which *K. lacertarum* Danil. is the type, are further remarkable for causing the nucleus of the corpuscle to become broken up and destroyed (Fig. 47); in the genus *Hæmogregarina sensu strictiori* the vermicule exceeds the corpuscle in length and is doubled up within it like a U or V (Fig. 48). Such differences can hardly be regarded as of generic importance, and it is best, for the present at least, to regard all the hæmogregarines as belonging to a single genus.

Till quite recently hæmogregarines<sup>1</sup> were believed to be confined to cold-blooded vertebrates, a number of forms being known from fishes, amphibia, and reptiles. The best known of these are *Hæmogregarina ranarum* (*Drepanidium ranarum* Lankester, *Lankesterella mimina* Auct.) from the frog, *H. (Karyolysus) lacertarum* Danil. from lizards, and *H. stepanowi*

<sup>1</sup> A list complete to date of the known species of hæmogregarines is given by Laveran (40).

Danil. from tortoises (*Emys lutaria* *Cistudo europea*). Recently, however,

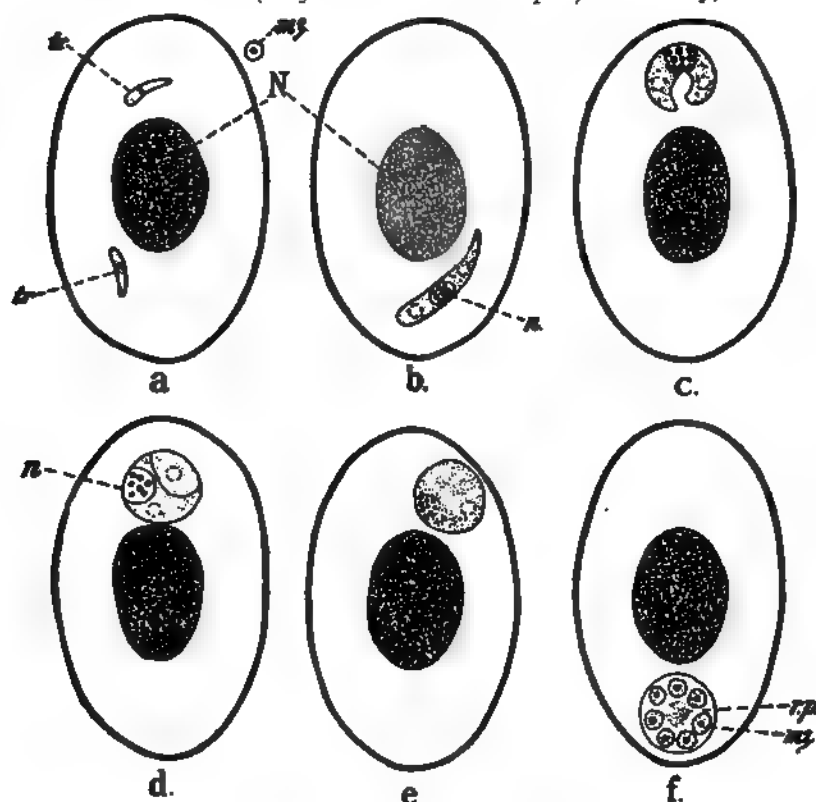


FIG. 46.—*Haemogregarina vasorum* Lank. in the blood-corpuscles of the frog. a, young stage; b, full-grown trophozoite; c, f, schizogony; m, merozoite; n, nucleus of parasite; N, nucleus of blood-corpuscle; tr, trophozoite; rp, residual protoplasm. From Minchin, after Hintze.

several species have been described from mammals. Such are *Haemogregarina gerbilli* Christophers from an Indian rat, *Gerbillus indicus*;

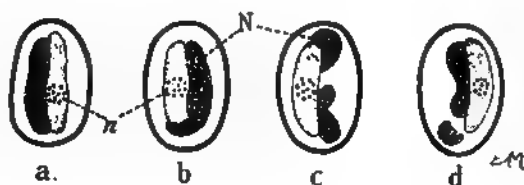


FIG. 47.—*Haemogregarina* (*Karyolus*) *loxotarsus* Danil. in the blood-corpuscles of the lizard *Lacerta muralis*, showing the manner in which the nucleus (N) of the corpuscle becomes broken up. n, nucleus of the parasite. From Minchin, after Maréchal.

*H. jaculi* Balfour (*H. balfouri* Laveran) from the jerboa; and the peculiar parasite discovered by Bentley in dogs and described by James under the

name *Leucocytozoon canis*. The last-named parasite differs from the typical hæmogregarines in being a parasite of the leucocytes. As such it recalls the *Leucocytozoon dunlewskyi* Ziemann and "*Hamamoba ziemanni*" Laveran, both from birds. The last-named is stated by Schaudinn to be a stage in a *Spirochaeta* (see p. 43), and the leucocytozoon of the dog may prove similarly not to be a true hæmogregarine. A similar parasite has been observed by Balfour in the leucocytes of *Mus decumanus*. The significance and systematic position of the leucocytozoa of birds and mammals are not at all clear at the present time. A human hæmogregarine has not yet been discovered.

The hæmogregarines of warm-blooded vertebrates appear in some cases to remain intracorpuscular so long as they are in the blood of the

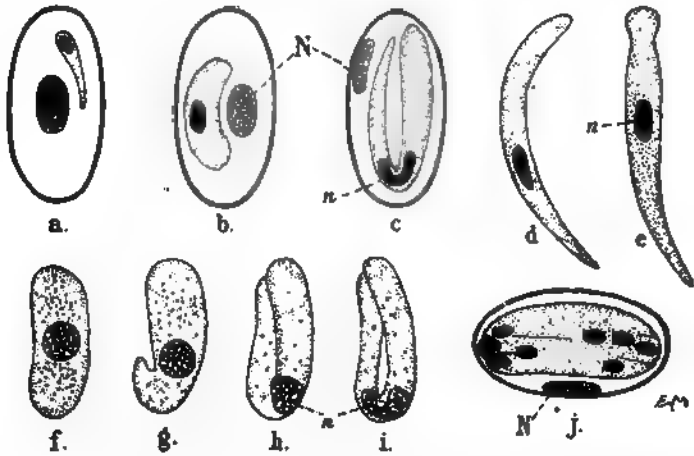


FIG. 48.—*Hemogregarina stepanovi* Danil. in the blood-corpuscles of tortoises. a, b, young trophozoites; c, full-grown trophozoite; d, e, the same free in the blood-plasma; f-i, to show the structure of the nucleus and the manner in which the vermicle form arises; j, sporulation. From Minchin, a and j after Laveran, f-i after Börner,  $\times 1000$ -1200 diameters.

host, only quitting the corpuscle and becoming motile when transferred to the invertebrate host, or when the blood is kept for some time *in vitro*. On the other hand the hæmogregarines of cold-blooded animals frequently quit the corpuscle and become free for a time in the blood-plasma, after which they may penetrate a blood-corpuscle again. Free stages appear to alternate in this way with intracorpuscular stages in a normal sequence. The free vermicles move forwards by means of gliding movements of the kind commonly observed in gregarines and gregarinoid individuals generally. In *Hemogregarina mirabilis*, a parasite of a snake *Tropidonotus piscator*, Castellani and Willey describe the intracorpuscular parasite as enveloped in a capsule or membrane, which it leaves behind in the corpuscle when it emerges into the blood-plasma.

The invertebrate host is known in but a few instances and was first discovered by Siegel (79) for *Hemogregarina stepanovi*. In the forms parasitic on aquatic vertebrates, such as fishes, frogs, tortoises, it appears

to be usually a leech. In the case of terrestrial vertebrates transmission is perhaps effected always by an arthropod. Schaudinn found the invertebrate host of *Karyolysus lacertarum* to be a tick, *Irodes ricinus*. Christophers found the sporogony of *Hæmogregarina gerbilli* in a louse, *Haematopinus stephensi*. It is highly probable that an intermediate host occurs in all cases, and that the resistant cysts described by Hintze for *H. ranarum* in the gut of the frog, were in reality the cysts of a coccidian and do not belong to the life-cycle of the hæmogregarine.

In *Hæmogregarina stepanowi* (Fig. 48) of tortoises the parasite occurs in two forms, one bean-shaped, the other slender and snake-like. The former are schizonts and multiply non-sexually in the tortoise to form merozoites, but undergo no further development in the leech. The snake-like forms are sporonts, which in the leech escape from the corpuscles, and produce gametes in the spaces between the villi of the intestine. The minuter details of the sporogony have not been described, but the microgametes are very minute. After fertilisation has taken place in the intestine, the motile oökinetes pass through the wall into the blood-space, and are then carried to the heart and finally penetrate into the œsophageal glands. During this process of migration the nucleus of the oökinete is undergoing multiplication, and in the salivary glands a process of sporulation produces a vast number of sporozoites, in the form of minute spirally-twisted filaments, which become free in the lumen of the gland and are capable of infecting the tortoise if the leech sucks its blood. Siegel found the sporozoites also in the œsophageal glands of immature embryos still subsisting on the yolk of the ovum, thus proving the existence of germinative infection.

Some interesting observations on the development of *H. gerbilli* in the louse were made by Christophers (19), who has not, however, described the complete life-cycle. The hæmogregarines quit the blood-corpuscle in the gut of the louse and pass through the gut-wall into the body-cavity. From the analogy of the parasite described in the foregoing paragraph the forms which pass through the gut-wall should be oökinetes produced by conjugation of gametes formed in the intestine, but this is not stated to occur. In the body-cavity the parasite rounds itself off and becomes a cyst, which grows from about 10  $\mu$  in diameter to as much as 350  $\mu$ . During the growth the contents of the cyst become divided into oval bodies, which become spore-like structures containing six to eight sausage-shaped sporozoites. The further development or migrations of the sporozoites was not traced, but they were found to exhibit active movements of a peculiar kind when placed in the blood of the *Gerbillus*, while the digestive juices of the latter had no marked effect upon them. It may be reasonably inferred, therefore, that the sporozoites are in some way inoculated by the louse into the *Gerbillus* and start a fresh cycle of the hæmogregarine. In the blood of the *Gerbillus* the parasite appears to multiply by longitudinal binary fission. In the case of the hæmogregarine of the jerboa, however, schizogony takes the form of multiple fission of the usual type.

(3) *Piroplasma* Patten (synonyms *Hæmatococcus* Babes ; *Babesia*<sup>1</sup> Starcovici ; *Pyrosoma* Smith and Kilborne ; *Apiosoma* Wandolleck) comprises a number of species parasitic in the blood of various mammals, but not known as yet in the blood of vertebrates belonging to other classes. All the known species exhibit great similarity both in morphological characters and in biological relations, and are scarcely distinguishable except in that they occur in different mammalian hosts. Nevertheless the species of *Piroplasma* appear to be greatly restricted in their occurrence, being each confined to a particular host, or to a group of hosts belonging to the same genus or family of mammals. As a general rule, *Piroplasma* is not inoculable into animals widely distinct from its proper host. If, however, Wilson and Chowning (86) are right in regarding *Spermophilus columbianus* as the natural host of *P. hominis*, we have an exception to the foregoing statement, and also another instance of a parasite being deadly to a host which is not its proper one.

The diseases produced by these parasites in their respective hosts are

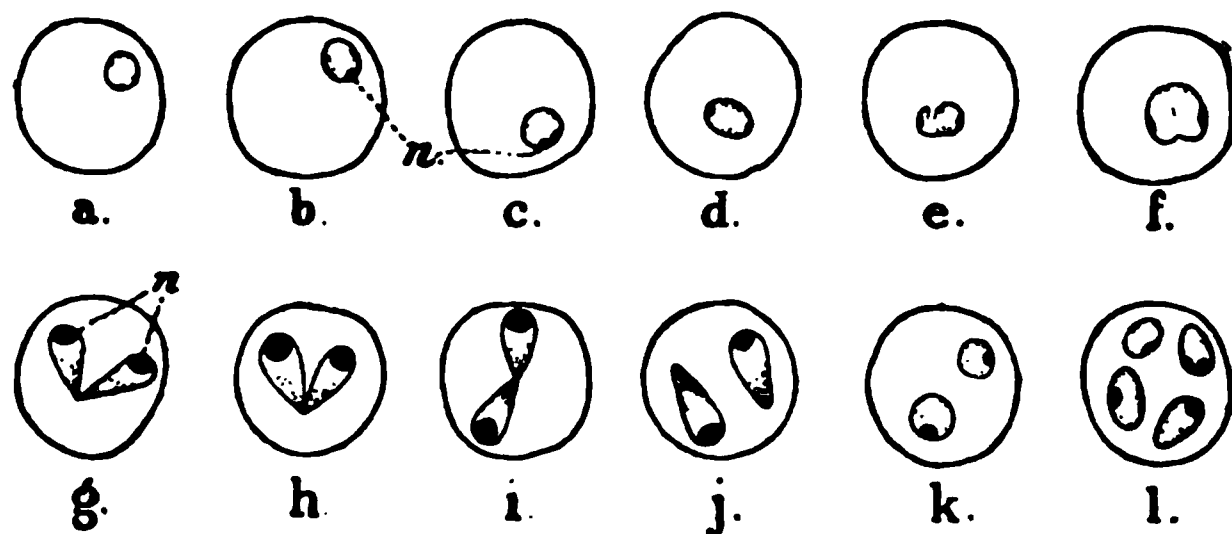


FIG. 49.—*Piroplasma bigeminum* in the blood-corpuscles of the ox. a-f, ring-forms and their multiplication by fission; g-j, pear-shaped forms; k, l, doubly infected corpuscles. From Minchin, after Laveran and Nicolle.

generally of very similar character, and may be termed collectively piroplasmoses. In their acute form the chief symptom is hæmoglobinuria consequent upon rapid destruction of blood-corpuscles. The invertebrate host has been found to be, without exception, some species of tick.

The best known and earliest discovered species are those which infest cattle, and produce in these animals a disease known by the great variety of local names. In America the disease is known as Texas fever or southern cattle fever, and the parasite was given the specific name *bigeminum* (Fig. 49) by Smith and Kilborne, whose memoir (81) marked an epoch in the literature of parasitic Protozoa, and first established the nature of the parasite and made clear the etiology of the disease. In Europe the parasite causing hæmoglobinuria of cattle was given by Babes the specific name *bovis*. It is not possible to state definitely at present whether *bovis* and *bigeminum* are to be ranked as synonyms or as names applying to distinct species, though the former opinion is the one most generally held. It has been clearly shewn, however, that a distinct

<sup>1</sup> The name *Babesia* has priority over *Piroplasma* and is the zoologically correct name of the genus ; see Minchin (53, p. 269) and Lühe (46).

species, to which Theiler has given the name *P. parvum*, is the cause of the fever of cattle on the East Coast of Africa, otherwise known as Rhodesian redwater, and occurring also in Transcaucasia, where it is known as tropical bovine piroplasmosis. *P. parvum* can be distinguished from the ordinary form of *bigeminum* both morphologically and also because oxen immune to the latter can be inoculated with the former. Other species of *Piroplasma* are *P. ovis* (Starcovici); *P. equi* (Laveran); *P. canis* Piana and Galli Valerio, and *P. muris* Fantham. An unnamed species parasitic on monkeys (*Cercopithecus*) has been described by P. H. Ross (72). Least satisfactorily known of all are the species alleged to attack man. According to Wilson and Chowning a *Piroplasma* to which Manson has given the name *P. hominis* is the cause of the so-called "spotted fever" or "tick fever" of the Rocky Mountains. As stated above, the Leishman-Donovan bodies are referred by some authorities to the genus *Piroplasma*, but perhaps incorrectly.

In the blood of the mammalian host the parasite is found in a number of different forms, of which the relation to one another, and their place in the general life-cycle of the parasite, is not at all clear. Most characteristic are the pear-shaped forms (Fig. 49, *g-j*), from which the parasite was originally named *Pyrosoma* by Smith and Kilborne, a name, however, long preoccupied for a genus of ascidians and hence superseded by *Piroplasma*. The pear-shaped forms vary considerably in size, and can generally be distinguished as small forms, 1 or 1.5  $\mu$  in length, and large forms 2-3  $\mu$  or more in length. In *P. bigeminum* they range from 1-3  $\mu$  in length, in *P. canis* they are slightly larger and may occasionally reach 4 or 5  $\mu$  in length. The greatest breadth is about one-third, or slightly less than the length. The cytoplasm appears denser towards the periphery, and clear, or even vacuolated, towards the centre. The nucleus is lodged at the broad end of the body and appears as a compact mass of chromatin, varying from .2 to .6 or .8  $\mu$  in diameter, round which a clear halo can often be seen. This appearance is regarded by some authors as representing a vesicular nucleus, and hence the central chromatin mass is often spoken of as a karyosome. Except as a preparation to division, the nucleus appears single; but, according to Lühe, a second chromatic body is always present, but is very minute, so that it has hitherto been overlooked, and is usually situated near the pointed end of the body.

The pear-shaped parasites occur singly or in greater numbers inside the blood-corpuscles. In *P. canis* the number of parasites in a single corpuscle may be twelve or sixteen, disposed quite irregularly (Fig. 54). A common arrangement is for the parasites to be in pairs, those of each pair often being connected at their pointed ends by a delicate filament of protoplasm, indicating multiplication by fission not quite completed. The twin arrangement is especially frequent in the bovine *Piroplasma*, which has hence received the specific name of *bigeminum* Smith and Kilborne. Another characteristic pattern is that in which four pear-shaped parasites are connected by their narrow ends, forming a cross.

Koch (35) considers this a morphological character of specific importance by which the parasite of African coast fever of cattle can be separated from the true *P. bigeminum*, and by which also two species of equine *Piroplasmata* can be distinguished.

The pear-shaped parasites, though generally of quite definite form, may in some circumstances become very irregular in form, throwing out pseudopodial processes from various parts of the body. There not infrequently appears to be the formation of a single long pseudopodium from the narrow end of the body (Fig. 52 A-C). The significance of this will be discussed presently.

Another form of the parasite is the spherical or ring form (Fig. 49, a-c), in which the centre of the body appears vacuolated, recalling the

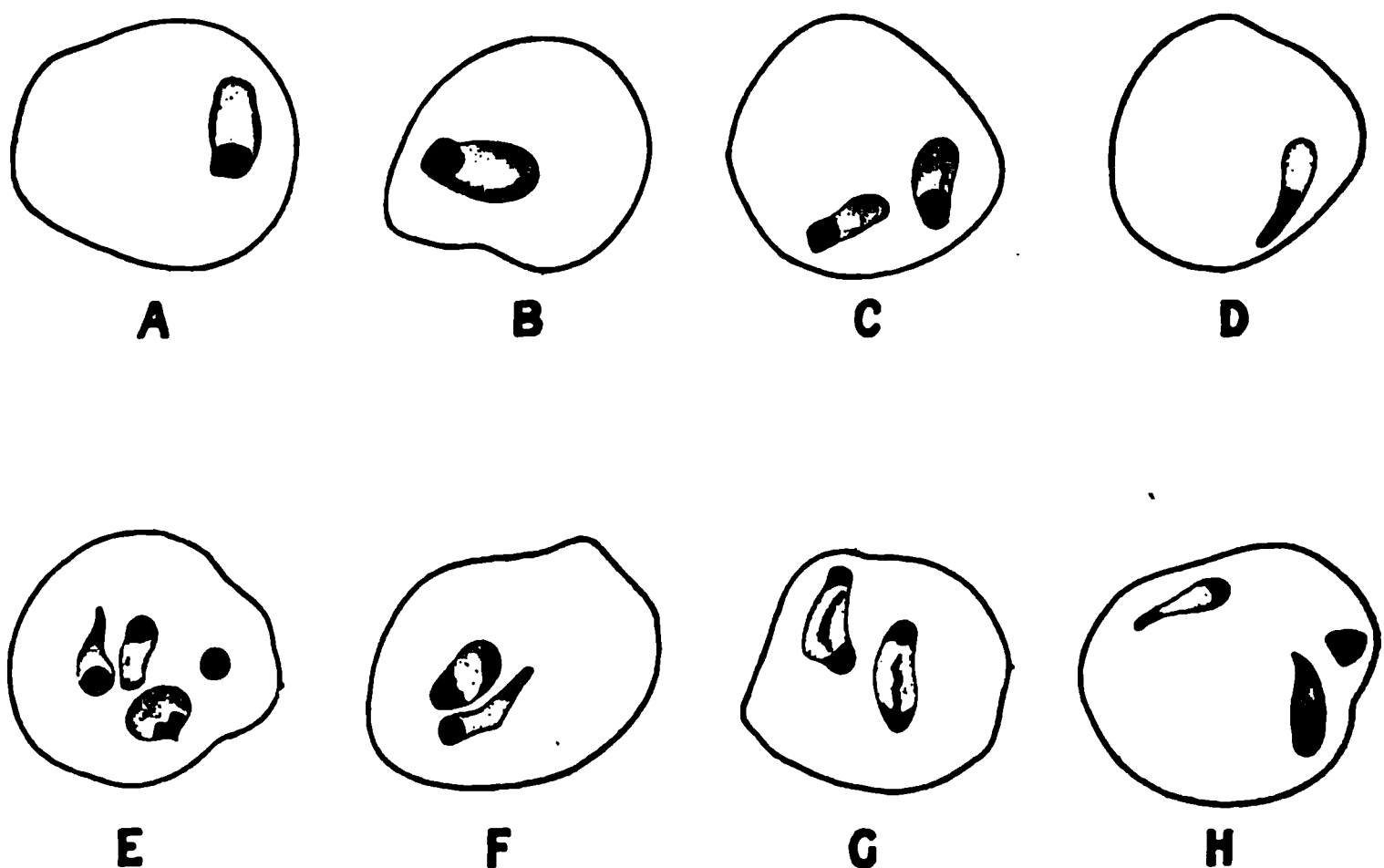


FIG. 50.—A-D, *Piroplasma bigeminum*, forms from the blood of immune oxen. E-H, *P. parvum* in the blood-corpuscles of an ox suffering from African East Coast Fever. After Theiler.

ring form of the malarial parasite, and the chromatin mass is generally placed quite at the periphery of the body, often projecting from it, or appearing almost as if detached from it.

A third form frequently found is the so-called bacillary form (Fig. 50), in which the body is rod-shaped, with the chromatin mass at one extremity. *Piroplasma parvum* Theiler, is characterised by appearing in the form of rings and rods, and never as the typical pear-shaped bodies. *P. bigeminum* may, however, also appear in this form, as described below. The bacillary form is perhaps to be regarded as a modification of the pear-shaped body. Finally, some authors describe coccus-like forms, which were found by Smith and Kilborne in mild cases of Texas fever, but some doubt is perhaps permissible as to whether these forms really belong to the cycle of the parasite.

All the above-described forms of the parasite are intracorpuseular in



habitat. Free forms also occur in the blood, as a result of the disintegration of corpuscles destroyed by the parasite. In *P. canis* free parasites are found sometimes in groups similar to those seen in the corpuscles. Among the free forms a specially noteworthy type is the so-called flagellate form described by Bowhill and Le Doux (7) in *P. canis* and *P. boris*, and by Bowhill (6) in *P. equi*. In this form of the parasite

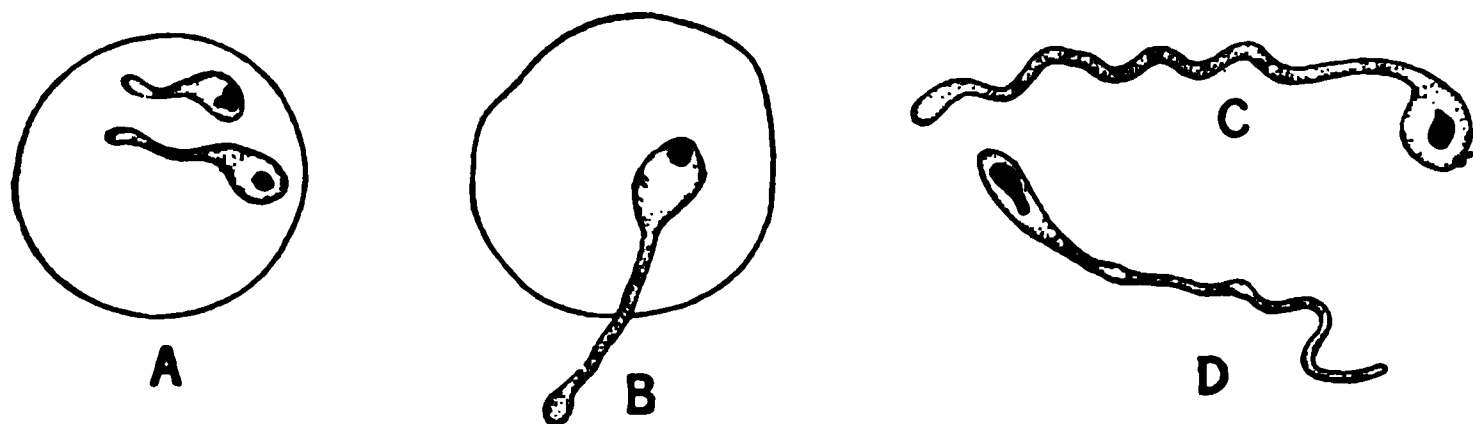


FIG. 51.—So-called flagellated forms of *Piroplasma*. A, two parasites in a corpuscle (*P. equi*); B, a parasite issuing from a corpuscle (*P. equi*); C and D, parasites free in the blood (*P. canis* and *P. boris* respectively). Drawn from photomicrographs given by Bowhill and Le Doux.

a long, slender filament issues from the pointed end of the pear-shaped body (Fig. 51, C, D). The filament is several times the length of the body; it runs an undulating course; and it is terminated by a bulbous enlargement, and may have one or two similar enlargements along it. From the last-mentioned peculiarity it seems clear that the filament is not a flagellum in the true sense of the word, and it may be compared with the long, slender pseudopodial process seen in the intracorpuseular forms, as described above. In one instance Bowhill (6, p. 10) observed a parasite with the pear-shaped body lodged in a corpuscle and the so-called flagellum passing out of it. I suggest that the “flagellum” is probably to be interpreted as a pseudopodium, by means of which the parasite may quit a corpuscle, and by means of which it may, when free, attack and enter another corpuscle. It is not possible, however, to give

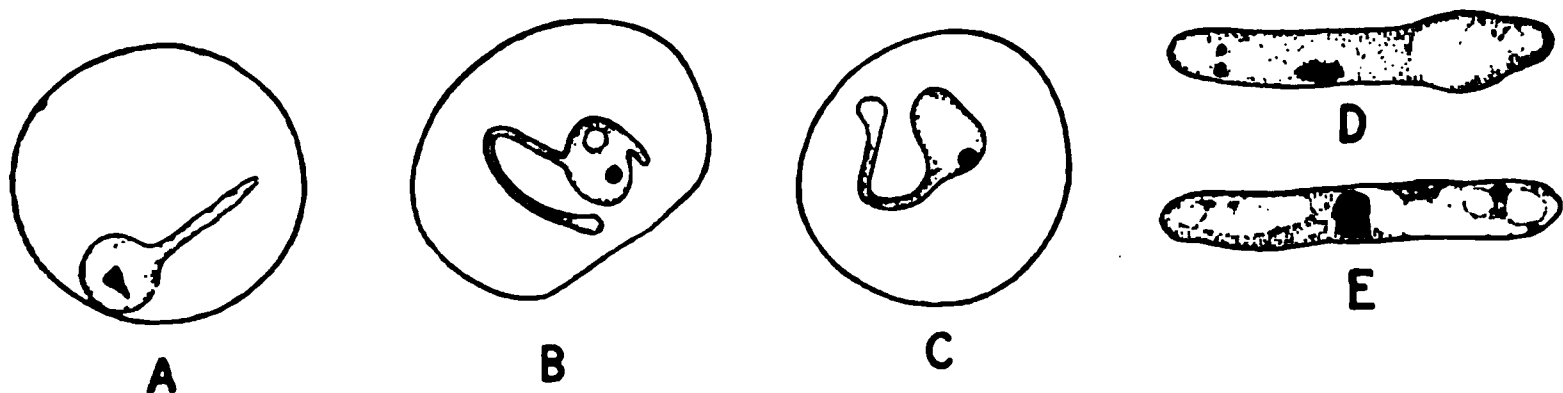


FIG. 52.—*Piroplasma canis*. A, B, C, parasites in blood-corpuscles of the dog, each showing a long pseudopodial process; D and E, supposed gametocytes. After Nuttall and Graham-Smith.

a final judgment upon this point until the so-called flagellum has been seen and studied in the living condition. Nuttall and Graham-Smith (58) describe free, sausage-shaped forms of *P. canis*, which they consider possibly to represent gametocytes (Fig. 52, D, E). Various forms have been interpreted in this sense by different authors, but in no case has the correctness of the interpretation been proved. It was suggested by Doflein that the pear-shaped forms might represent gametocytes, and the



spherical forms schizonts. The observations of Koch (35), described below, give some support to the first of these two suppositions.

The endogenous multiplication of the parasites appears to take place always by binary fission, which in the pear-shaped forms is longitudinal

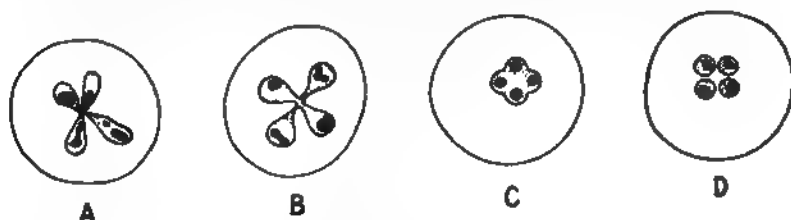


FIG. 53.—Multiple fission of *Piroplasma equi*. A and B, cross-forms; C and D, fission. A and B after Bowhill, C and D after Laveran.

in direction. The cross-forms mentioned above, however, may owe their origin either to simultaneous multiple fission into four, such as Laveran has described in *P. equi* (Fig. 53, C, D), or to two rapid successive binary fissions. Smith and Kilborne found the percentage of infected corpuscles very much greater in the capillaries of the heart-muscle and in some of the internal organs, especially the kidneys, indicating a more rapid multiplication of the parasites in these parts.

Theiler (83) has made some interesting observations on the latent form of *P. bigeminum* in the immune ox (Fig. 50, A-D). When an ox has recovered from an attack of piroplasmosis it remains immune against further infection or inoculation by the same species of parasite. Never-

theless the parasite remains in the blood, as proved, first, by the fact that the animal is liable to a relapse; secondly, by the fact that the blood of immune ox injected into a susceptible animal causes the typical pear-shaped *Piroplasma* to appear in the latter and brings on an attack of the disease. In the immune ox *P.*

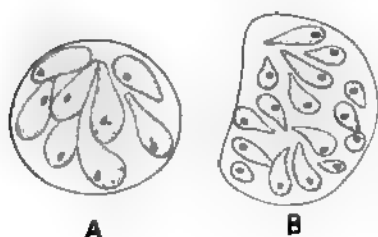


FIG. 54.—A and B, *Piroplasma crass*, numerous parasites in blood-corpuscles of the dog. After Nuttall and Graham-Smith.

*bigeminum* is present in the blood as bacillary and ring like intracorpuseular forms, very similar, though in reality quite distinct from the form under which *P. parvum* appears (Fig. 50, E-H).

As stated above, the invertebrate host of every species of *Piroplasma* hitherto investigated has proved to be a tick. A given species of *Piroplasma* may be transmitted by more than one species of tick, in the same or different parts of the world.

The only observations upon the development of *Piroplasma* within the tick are those of Koch (35), whose statements and descriptions are difficult to interpret. Koch studied the development of *P. bigeminum*

(Smith and Kilborne) and of the parasite of bovine east coast fever (*P. parvum*). The stages seen were for the most part similar in the two cases, only rather smaller in the second of the two parasites mentioned.

When taken up by the tick the pear-shaped parasite leaves the blood-corpuscle after its chromatin mass has divided into two. The parasite becomes elongated, and one chromatin mass places itself at the "anterior" end, by which is meant, apparently, the blunt end of the pear-shaped parasite, where it forms a deeply staining point or apex projecting sharply forward. The other chromatin mass remains in the middle of the body. Next, ray-like processes arise near the apex, first two or three, then more. These form a star-like figure surrounding the apical chromatin mass (Fig. 55, B). It is not clear whether these processes are to be regarded as flagella or as pseudopodia.

In favour of the former interpretation would be their origin from a mass of chromatin, but their stiff, sharp form, tapering gradually from their base to a sharp point, and their irregular arrangement make it more probable that they are to be regarded either as pseudopodia or perhaps as cuticular spikes. Parasites of this form tend to form groups, and from the second day onwards they are frequently to be found fusing in couples by their posterior ends, giving rise to bodies in which a star of radiating processes arise from each end of the body (Fig. 55, C). This stage is succeeded by one in which the body is spherical, containing chromatin attached in patches to the interior of the limiting membrane, and with a spike of chromatin at the periphery (Fig. 55, D). Such forms are derived apparently from zygotes which have lost their radiating processes and become rounded off. These bodies appear to be succeeded by elongated, oval, or pear-shaped forms with a fairly large nucleus of similar consistence, which are probably transitional to the pear-shaped forms, each three or four times the size of a *Piroplasma* in the blood, occurring in the eggs of infected ticks (Fig. 55, E, F). The transition from the last-named to the *Piroplasma* of the ox has not been traced.

(4) *Halteridium* Labbé (synonym *Hæmoproteus* Kruse). This well-known parasite of birds is generally included amongst the malarial

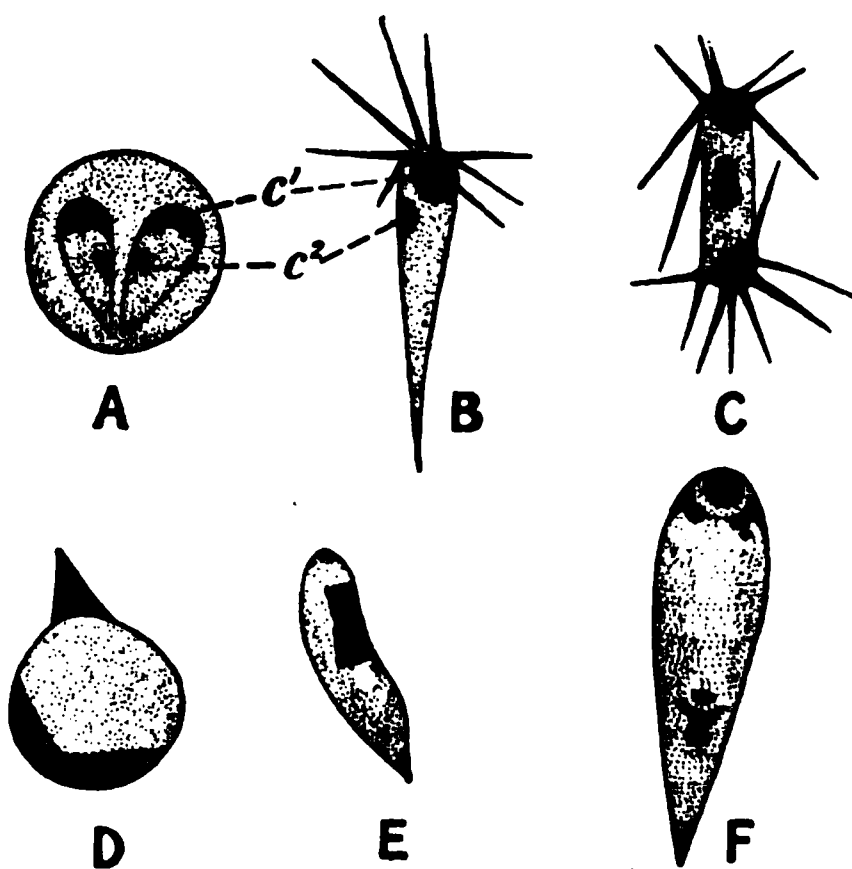


FIG. 55.—Stages in the development of *Piroplasma bigeminum* in the tick. A, division of the nucleus ( $c^1$ ,  $c^2$ ) in the twin intracorporeal parasites; B, free club-shaped forms with radiating processes; C, apparent conjugation of two forms like B; D, rounded form with a deeply staining spike at one point; E, pear-shaped form; F, large pear-shaped form found in the egg of the tick. After Koch.

parasites, though considered by most authors generically distinct from the forms included under *Plasmodium* (= *Hæmumæba*); but the recent researches of Schaudinn (75) on the life-history of *Halteridium*, if the facts are as alleged by him, throw quite a new light on the affinities of this form. *Halteridium* resembles *Plasmodium* in producing melanin-pigment, but unlike the latter it has a more or less definite shape and is very slightly amœboid. It is easy to distinguish *Halteridium* (Fig. 56) by morphological characters from *Plasmodium præcox* (Fig. 45) occurring with it in birds. While the *Plasmodium* occupies nearly the centre of the corpuscle as a more or less compact amœboid body which displaces the nucleus, the *Halteridium* remains to one side of the nucleus which is not displaced, but the parasite grows round it like a halter, hence the generic

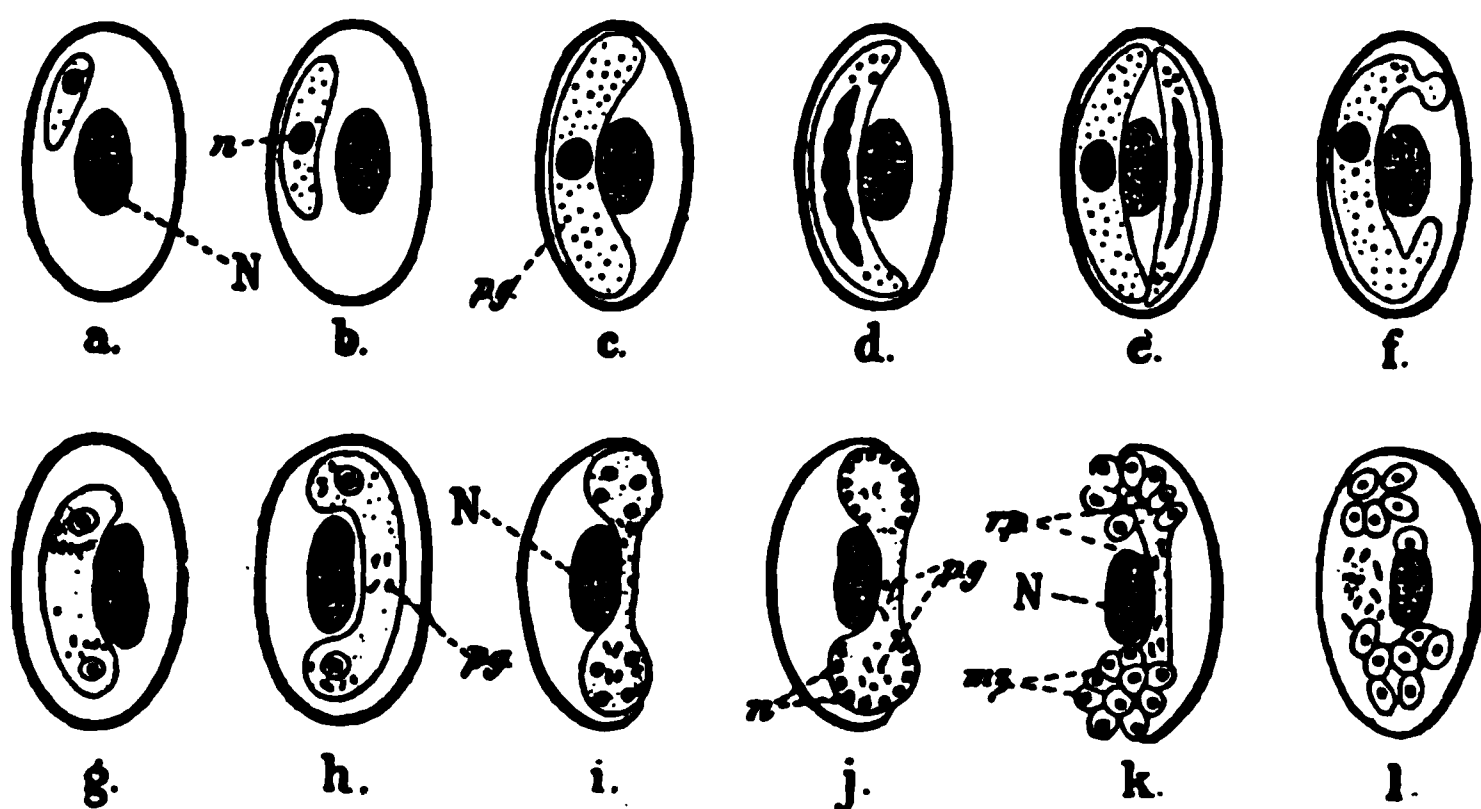


FIG. 56.—*Halteridium danilevskyi* Kruse, in the blood-corpuscles of various birds. a and b, young trophozoites; c, female; d, male gametocyte; e, both in one corpuscle; f, female gametocyte throwing out pseudopodia; g-l, schizogony; n, nucleus of parasite; N, of corpuscle; p.g. granules of melanin-pigment; r.p., residual protoplasm; m.z., merozoites. From Minchin; a-f after Laveran, g-l after Labbé.

name which it bears. *Halteridium*, as such, is an exclusively intracorpuscular parasite, but as described above, it is stated by Schaudinn to become free in the blood as a *Trypanosoma*, of which it should be regarded merely as the resting stage (Fig. 8). Labbé described a process of sporulation in *Halteridium* which has not been seen by subsequent investigators (Fig. 8, g-l). The invertebrate host, according to Schaudinn, is a *Culex*. It was in *Halteridium* that MacCallum first observed the fertilisation, and demonstrated that the so-called flagella of malarial parasites were really microgametes. According to Schaudinn, MacCallum's observations were substantially correct, but he did not notice the minuter details of structure (undulating membrane, etc.) in the microgametes.

GENERAL REMARKS ON THE HÆMOSPORIDIA.—The foregoing description of the four generic types of Hæmosporidia bears out the statement made above that they have little in common. In *Plasmodium*, which is the most accurately known, and which may be taken as the type of the order, the entire development appears to be modelled, so to speak, on

the coccidian plan, with only such differences as can be explained by adaptation to a different mode of life and a special method of dissemination. In *Hæmogregarina* the development is not yet known in all its details, but so far as conclusions can be drawn from the recorded observations, there is nothing to indicate a separation from *Plasmodium* greater than would be brought about by placing the two genera as types of distinct families. The stages of *Hæmogregarina gerbilli* described by Christophers in the invertebrate host appear to be even more coccidian in character than the exogenous cycle of *Plasmodium*. On the other hand the whole life-cycle of *Piroplasma* differs, so far as can be judged at present, in all stages from *Plasmodium*, and bears no obvious affinity to that of any known type amongst the *Telosporidia*. *Piroplasma* must be considered at present, as a genus entirely apart, of which the affinities are not yet established.

As regards *Halteridium* also, the life-cycle described by Schaudinn does not permit of any comparison with that of *Plasmodium*, and suggests that the former genus has been erroneously referred to the Hæmosporidia. On this point it is necessary to suspend judgment until Schaudinn's statements have received adequate confirmation. Billet asserts, however, that a species of *Lankesterella* (*Hæmogregarina*) occurring in Algerian frogs is a stage in the life-cycle of *Trypanosoma inopinatum* occurring in the same host. These facts have led many authorities to consider the Hæmosporidia and Hæmoflagellates to be very closely allied, and Lühe considers that these two groups form "not merely a biological but a systematic unity." Even assuming, however, the perfect correctness of the statements made by Schaudinn with regard to the life-cycle of *Halteridium*, and of Billet with regard to *Lankesterella*, it seems to me not justifiable in the present state of knowledge to regard the Hæmosporidia and the Hæmoflagellates as a single natural group, in view of the close resemblance of the life-cycles of the malarial parasites and the coccidia, a resemblance which was clearly established by Schaudinn, and which led Mesnil to go so far as to classify the malarial parasites as a subdivision of the coccidia. The tendency of recent researches would seem rather to indicate that the Hæmosporidia so-called are not a natural group, and that many forms referred to it are, like the Leishman-Donovan bodies, merely resting stages in the life-cycle of Flagellata.

Sub-class II.—*Neosporidia*.—Sporozoa in which spore-formation generally commences and proceeds during the trophic phase of the parasite, trophozoites hence multinucleate; spore-mother-cells formed in the interior of the body of the parasite (hence Endosporées Metchnikoff); swarm-spore usually an amœbula.

The foregoing definition may be taken as indicating in a general way the distinctive characters of the Neosporidia as compared with the Telosporidia, but like all hard and fast definitions of systematic groups, it may require, as will be seen, certain modification of detail in its application to particular cases; especially as regards the first character, namely spore-formation during the trophic phase.

The Neosporidia comprise five orders, the Myxosporidia, Actinomyxidia, Microsporidia, Sarcosporidia, and Haplosporidia. By many authorities the order Myxosporidia is used in a wider sense, to include the Microsporidia, and the whole order is then divided into two sub-orders, Phænocystes and Cryptocystes; the former are the Myxosporidia in the strict sense, the latter are the Microsporidia. Hence in using the name Myxosporidia it is necessary to understand clearly whether it is used in the wider or in the narrower sense. In the present article it will be employed in the latter manner, and the Microsporidia will be treated as a distinct order.

Order I. —*Myxosporidia sens. strict.*—The trophozoite is amoeboid and Rhizopod-like; the spores are relatively large and bilaterally symmetrical, and have two or four "polar capsules," which are plainly visible in the fresh condition of the spore (hence Phænocystes Thélohan).

The numerous forms comprised in this order are for the most part, though not exclusively, parasites of fishes, whence they are commonly termed "fish-psorosperms" in older works, a term applied more particularly to their conspicuous spores. They occur also in amphibia and reptiles, though sparingly, but are not known as yet in any warm-blooded vertebrate. In invertebrates their occurrence is very exceptional.

In the bodies of their hosts the Myxosporidia are either cœlozoic or histozoic in habitat. The youngest parasites, however, in either case, are probably of intracellular habitat. The cœlozoic forms are found chiefly in the cavities of the biliary or urinary organs, that is to say in the gall-bladder, bile-ducts, urinary bladder, or kidney tubules. No species are known to occur in the lumen of the digestive tract or in the

general body-cavity of the host, like gregarines. In the cavities in which they occur they may float freely, or be attached by their pseudopodia to the lining epithelium. The histozoic forms occur as intercellular parasites of various tissues, especially of connective or muscular tissue, sometimes also nervous tissue. In the tissue attacked by them they may be concentrated at one spot forming a cyst usually visible to the naked eye

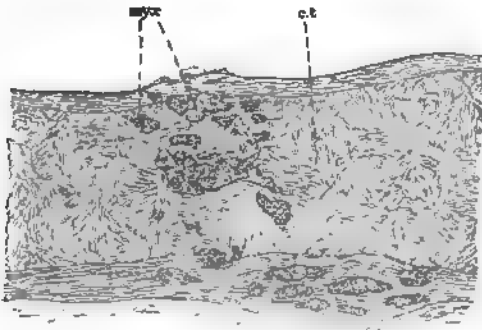


FIG. 57.—Section of the wall of the urinary bladder of a tench, showing *Myxidium elipiculus* Thel. (myx) occurring in the condition of diffuse infiltration between the bundles of connective tissue (c.t.). From Machin, after Thélohan.

(compare Fig. 64), or they may occur in the condition known as diffuse infiltration (Fig. 57), in which the parasite and the tissue have grown together so intimately that microscopic examination is necessary in order to distinguish them. Since the body of the parasite very soon becomes

converted for the most part into spores, sections of infected tissue shew it to be infiltrated with the characteristic "psorosperms." The tissue-infecting Myxosporidia often cause ravaging epidemics among freshwater fish.

The adult, that is to say, spore-forming trophozoite, is generally large and amoeboid, with the body distinctly divided into hyaline ectoplasm and granular endoplasm (Fig. 58). The ectoplasm is the seat of movement, all pseudopodia taking origin from it, and is probably also protective in function, enabling the parasite to resist the action of the juices of the host. Sometimes the ectoplasm is converted temporarily into a vertically striated layer, as in *Myxidium lieberkuehnii* of the pike (Fig. 59), a condition interesting for comparison with the Sarcosporidia (see p. 104). The endoplasm contains, besides granulations of divers kinds, the nuclei and the spores, both usually numerous. In some species, however, spores may be formed only at certain seasons. For instance, in *Myxidium lieberkuehnii* spores are formed during the warmer months of the year, and in the winter the parasites usually contain no spores but many nuclei. During this season they multiply endogenously by separation off from the body of smaller masses of protoplasm, each of which

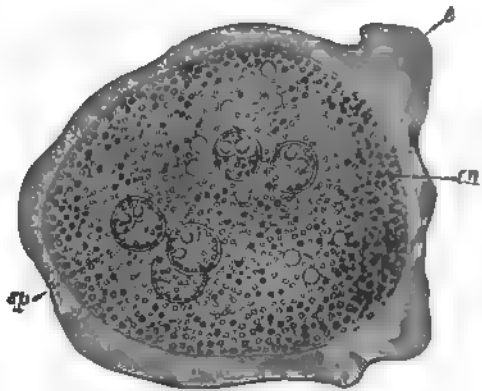


FIG. 58. - Amoeboid trophozoite of *Sphaerospora divergens* Thel., parasitic on fishes of the genera *Blennius* and *Trentulobus*. e, ectoplasm; en, endoplasm; sp, spores, of which five are seen. After Thelohan, from Wasielewski, x750.

grows to its full size; a form of germination for which Doflein has proposed the term *plasmotomy*. The spores of Myxosporidia exhibit very distinctive characters, both structural and developmental, combined with the utmost variation in form and external appearance. The fully-formed spore (Fig. 60) is of fairly large size and enclosed in a tough, resistant spore-membrane which has the form of two valves meeting in a suture. When the spore germinates in a new host, the envelope splits along the sutural line. Within the membrane are contained the sporoplasm and the polar capsules (Fig. 61).

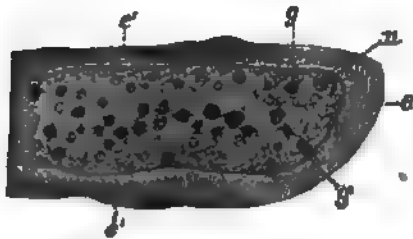


FIG. 59. - Extremity of a trophozoite of *Myxidium lieberkuehnii* from the urinary bladder of the pike, showing ectoplasm (e) vertically striated (at e' e'); n, nuclei; g, fat-globules. From Minchin, after Thelohan.

grows to its full size; a form of germination for which Doflein has proposed the term *plasmotomy*. The spores of Myxosporidia exhibit very distinctive characters, both structural and developmental, combined with the utmost variation in form and external appearance. The fully-formed spore (Fig. 60) is of fairly large size and enclosed in a tough, resistant spore-membrane which has the form of two valves meeting in a suture. When the spore germinates in a new host, the envelope splits along the sutural line. Within the membrane are contained the sporoplasm and the polar capsules (Fig. 61).

The latter are pear-shaped bodies, two or four in number, disposed in various ways, but always with the pointed end vertical to the surface of the spore. Under the action of certain stimuli a delicate filament is shot out of the capsule, after the manner of the trichocysts of Ciliata or the nematocysts of Coelenterata. The filament can be seen as a coiled thread in the undischarged capsule, giving it a striated appearance. The natural stimulus to the discharge of polar filaments is the digestive juice of the proper host, and the function of the filaments is to attach the spore to the epithelium of its digestive tract. The sporoplasm is a rounded mass of protoplasm generally occupying about half the interior of the spore. It contains two nuclei and sometimes also a vacuole.

The spores arise from spore-mother-cells or pansporoblasts (see above), each formed by a concentration of the protoplasm round one of the nuclei

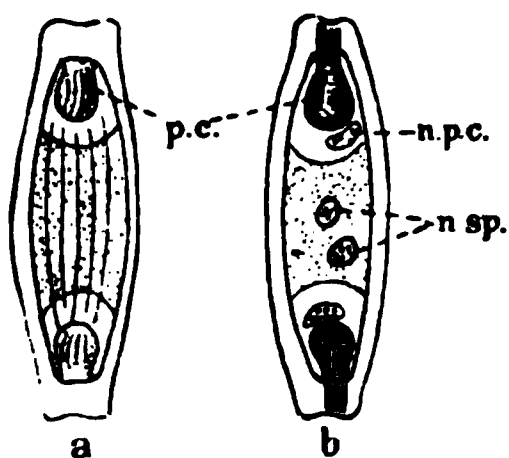


FIG. 60.—Spores of *Spharomyxa balbiani*. *a*, in the fresh condition; *b*, fixed and stained, shewing nuclei: *p.c.*, polar capsules; *n.p.c.*, their nuclei; *n.sp.*, nuclei of sporoplasm. From Minchin, after Thelohan,  $\times 1500$ .

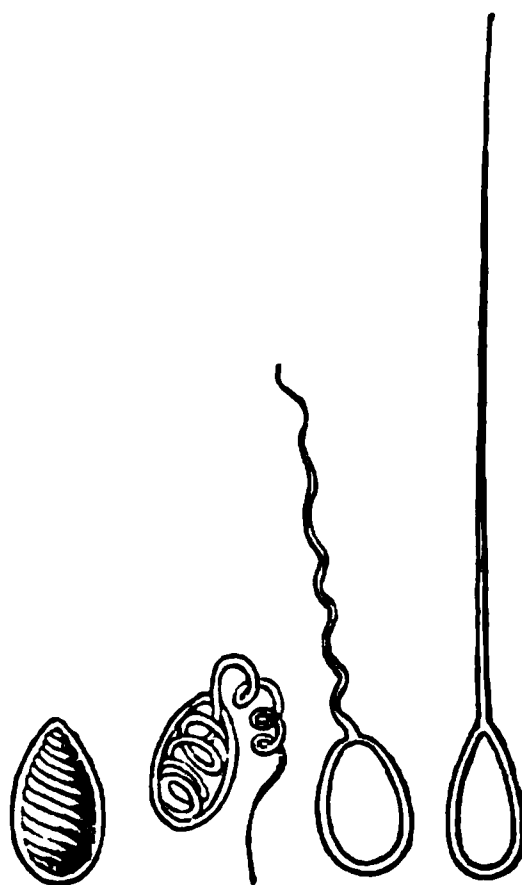


FIG. 61.—Polar capsules of *Myxobolus ellipsoides*, to shew the ejection of the filament. After Balbiani.

in the endoplasm of the parent trophozoite (Fig. 62). The pansporoblast becomes surrounded by a delicate envelope or pellicle, and its nucleus divides till ten or twelve nuclei are formed, some of which soon begin to degenerate. At the same time the pansporoblast grows in size, and when a limit of growth has been reached, it divides within the pellicle into two masses of protoplasm, representing two sporoblasts. Each sporoblast contains three nuclei, the remaining nuclei of the pansporoblast having degenerated and been cast out. Round each sporoblast the tough spore membrane begins to be secreted, and within the membrane the protoplasm divides into three masses, one larger, two smaller, centred round each of the three nuclei. The larger mass of protoplasm becomes the sporoplasm, and its nucleus divides into two. The two smaller masses of protoplasm are termed capsulogenous cells, and give rise each to a polar capsule. In the species, however, in which four polar capsules

are formed there are four capsulogenous cells, five nuclei are present in the sporoblast, and some fourteen or so in the pansporoblast. In a few rare cases one of the two polar capsules may be markedly smaller than its fellow, or only a single capsule may be formed.

The development of the adult trophozoite from the spore is the part

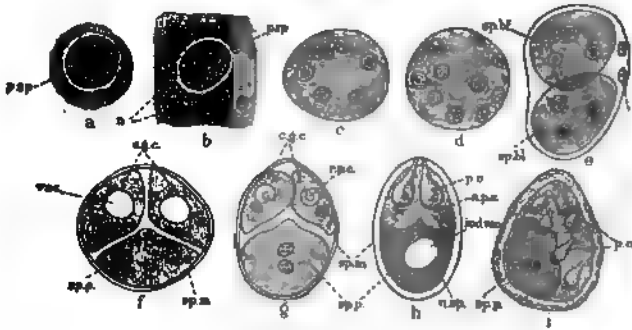


FIG. 62.—Spore-formation in Myxosporidia. a, differentiation of the pansporoblast (p.sp.); b, c, d, growth of the pansporoblast and multiplication of its nuclei; in c and d the protoplasm in which the pansporoblast is embedded is not shown; in d four of the nuclei are degenerating; e, division of the pansporoblast into two sporoblasts (sp.b.), each with three nuclei; r.n., residual nuclei; f, a single sporoblast or spore produced from it; g, the spore-membrane (sp.m.) now formed encloses two capsulogenous cells (c.g.c.), each with a vacuole (vac.) and the sporoplasm (sp.p.); the nuclei are not shown; h, formation of rudiments of the polar capsules (r.p.c.) from the vacuoles of the preceding stage; i, complete spore, with two polar capsules (p.c.), each with the remains of the nucleus (n.p.c.) of the capsulogenous cells, and with sporoplasm containing two nuclei (n.sp.) and an iodine-staining vacuole (iod.vac.); j, abnormal spore with numerous polar capsules. From Minchin, after Thelohan.

of the life-history least satisfactorily known, as is the case in most other sporozoa. Thelohan's ingenious experiments shewed that the spores, when swallowed by the host, germinate in the digestive tract. First the polar filaments are extruded, then the spore-envelope splits open, and the sporoplasm creeps out as a binucleate amoebula. Attempts to bring about infection in other ways gave negative results. If, however, the spore-contents are normally liberated in the intestine, it is evident that in most cases the amoebulae must undertake very extensive migrations in the body of the host to reach the organs or tissues in which they occur. In the carp after infection with *Myxobolus cyprini*, Doflein found, in the epithelial cells of the kidney, minute amoebulae multiplying actively by fission (Fig. 63), and it is probable that the great number of parasites often present is due to rapid endogenous multiplication of minute swarm-spores. It may be inferred that the first period of the life-history is one of active multiplication succeeded by a period of growth during which the numerous minute parasites cease to divide further, and develop into the adult spore-forming trophozoites. It is probable, however, that events other than simple proliferation occur during the early period

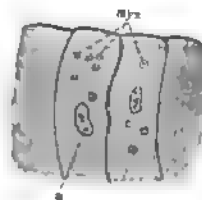


FIG. 63.—Kidney cells of the carp, filled with minute germs (myx) of *Myxobolus cyprini* multiplying rapidly. n, nuclei of the kidney-cells. From Minchin, after Doflein.



of the life-history. The youngest trophozoites observed, have a single nucleus, while the amœbula liberated from the spore is binucleate. It is highly probable that some process of conjugation takes place in the early stages of the development, comparable to the conjugation between swarm-spores which occurs so commonly in Sarcodina.

The Myxosporidia are divisible into two sub-orders. In the Disporea each trophozoite forms but a single pansporoblast, and therefore only two spores; the rest of the body of the trophozoite with its nuclei degenerates as residual protoplasm. In the Polysporea each trophozoite produces numerous pansporoblasts and twice as many spores. The Disporea includes two genera, *Ceratomyxa* Thél. and *Leptotheca* Thél., the species of which inhabit for the most part the gall-bladder of fishes, but *Leptotheca renicola* Thél. occurs in the kidneys of the common European frogs *Rana esculenta* and *R. temporaria*. The Polysporea comprise numerous genera and species, of which the following are amongst the best known:—*Myxidium*, characterised by fusiform spores with a polar-capsule at each end; *M. lieberkuehnii* Bütschli from the urinary bladder of the pike is a species usually easy to obtain; *Chloromyxum* Mingazzini with four polar capsules, type *C. leydigi* Ming. from the gall-bladder of the dog-fish and other Elasmobranchs; and *Myxobolus* Bütschli, of which numerous species are found in the connective tissue of the skin or other organs of various fishes, and are often the cause of deadly epidemics amongst them.

Order II.—*Actinomyxidia*.—This group was founded by Stolč to include certain very peculiar parasites, of which the exact position in classification has been a matter of dispute. In all four genera are known: *Synactinomyxon* Stolč, *Hexactinomyxon* S., *Triactinomyxon* S., and *Sphæractinomyxon* Caullery and Mesnil; and all the species hitherto discovered are parasitic on oligochæte worms of the family *Tubificidæ*. The recent investigations of Caullery and Mesnil (14) make it clear that these parasites must rank amongst the Neosporidia as a distinct order allied to the Myxosporidia. The trophozoite at the term of its growth and development consists of a binucleate envelope, representing residual protoplasm, containing eight spores. Each spore has a ternary symmetry, being enclosed by an envelope composed of three valves, and containing three distinct polar capsules. In the first three genera mentioned above, the valves of the spore are prolonged into tails or processes, but in *Sphæractinomyxon* the spore is spherical, without any prolongations. The sporoplasm may be either a plasmodial mass containing very numerous nuclei, or may be divided up into a large number of sporozoite-like bodies. Caullery and Mesnil have shewn that the spore-envelopes are developed separately from their contents in a remarkable manner; the former arise from a small mass of protoplasm containing six nuclei, which becomes divided into six cells, and three of the cells form the three valves of the spore, the other three the polar capsules. When the envelope is nearly complete, the sporoplasm migrates into it. The development of these organisms shews perhaps the nearest approach to distinct tissue-formation among any Protozoa. For further details, which would be out of place here, the

reader is referred to the memoir of Caullery and Mesnil (14) and the authorities cited therein.

Order III.—*Microsporidia*.—Trophozoites more or less distinctly ameboid; spores minute, pear-shaped, with a single polar-capsule, which is not visible in the fresh condition of the spore (hence *Cryptocystes* Thélohan).

The Microsporidia are typically cell-parasites, which infest chiefly invertebrate hosts, and especially arthropods. The best-known example of the order is *Nosema bombycis* Nägeli of the silk-worm disease. They may, however, occur in other invertebrates of various classes, and also in fishes, but they are not known as yet in any warm-blooded vertebrate.<sup>1</sup> *Pleistophora veriplancti* of the cockroach is exceptional in being, according to Perrin, an extra-cellular (i.e. celozoic) parasite occurring chiefly in the lumen of the Malpighian tubules.

The trophozoites in this order are of two very distinct types. In one type, that of *Thelohanus*, *Pleistophora* (Fig. 69), etc., the parasites are minute rounded bodies of microscopic size, which contain one or more nuclei, and occur within cells. Such forms may reproduce by schizogony, which can take the form of binary or multiple fission, or of plasmotomy, and are then termed "meronts" (Fig. 65); or they may proceed to spore-formation, and are then called sporonts (Fig. 66). There is little to distinguish the meronts and sporonts of this type from a Coccidian or other Telosporidian

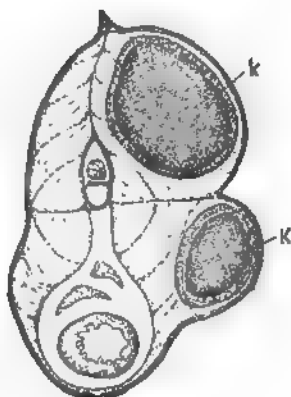


FIG. 64.—Transverse section of a stickleback (*Gasterosteus aculeatus*) showing two cysts (*k, k'*) of *Glugea anomala* Moniez in the body-musculature. From Muchin, after Thélohan.

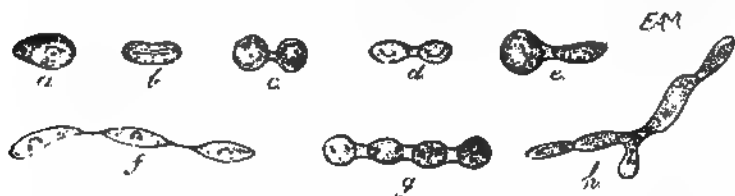


FIG. 65.—Schizogony of *Thelohanus nelleri* (L. Pfr.). *a*, meront with single nucleus; *b* and *c*, its division into two; *d*, *e*, into four; *f*, *g*, *h*, chains of meronts formed by rapid division. From Muchin, after Stenpell, x2250.

parasite, except the characteristic structure of the spores, and the fact that the spores arise in the interior of the sporont, imbedded in the protoplasm which is left over as residuum (hence Endosporées, Metchnikoff), and are not formed by superficial sporulation as in Telosporidia.

<sup>1</sup> The occurrence of a microsporidian parasite in man is asserted by Perroncito in a memoir which I have not been able to see (*Giorn. Acad. Med. Torino*, lxx. 1902, p. 378).

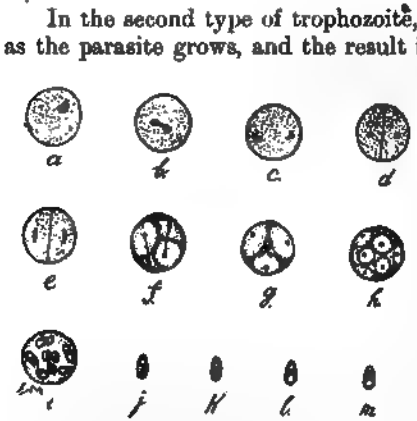


FIG. 66.—Spore-formation in *Thelohania muelleri* (L. Pfe.). a-d, division of the sporont into two; e-g, division into four. h, sporont with eight sporoblasts; i, eight spores imbedded in the residual protoplasm of the sporont; j-l, division of the nucleus of the spore; m, spore with four nuclei after three days in the gut of a new host. From Minchin, after Steimpell,  $\times 2250$ .

In the second type of trophozoite, that of *Glugea*, the nuclei multiply as the parasite grows, and the result is a large multinucleate trophozoite comparable to a Myxosporidian parasite. This type produces cysts distinctly visible to the naked eye, as in the common *Glugea anomala* of the stickleback (Fig. 64). The body of the parasite is enclosed in a cyst-envelope or *tunica propria* secreted by it, outside which the tissues of the host form a capsule of connective tissue (Fig. 67). The trophozoite soon outgrows the limits of a single cell, and is to be regarded as of histozoic habitat.

The nuclei of the trophozoite are at first vegetative in function, and may grow to a very large size; from them are produced small nuclei, round which the proto-

plasm becomes concentrated and separated off by a membrane from the remainder of the protoplasm, to produce by a process of internal

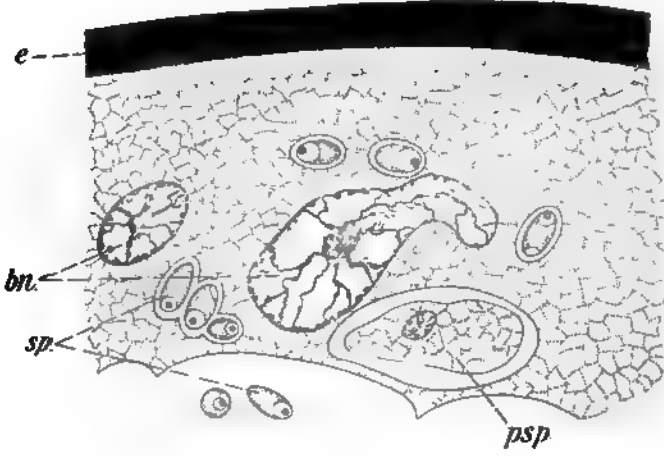


FIG. 67. *Glugea anomala* Monez, part of a section of the wall of a cyst. e, envelope; bn, vegetative nuclei; sp, spores; psp, sporont or pansporoblast, lying in a space in the protoplasm. After Steimpell.

gemination, a uninucleate individual which forms spores, and which is exactly comparable to the sporont of the first-mentioned type. It is evident, however, that the sporonts thus formed by internal budding are

also perfectly comparable to the pansporoblasts of the Myxosporidia. The homology of sporont and pansporoblast is sometimes expressed by saying that in *Pleistophora* and its allies the whole trophozoite becomes a single pansporoblast. It is perhaps better, however, to regard the condition of *Pleistophora* as primitive rather than secondary, and to consider the pansporoblasts of *Glugea* and of the Myxosporidia as sporonts produced by internal gemmation in the vegetative trophozoite. In *Thelohania* or *Pleistophora* there is no nutritive protoplasm surrounding the sporont, and the vegetative activity is shewn only in schizogony. The transition from this type to that of *Glugea* and the ordinary Myxosporidia is seen in the disporous Myxosporidia, where the multinucleate trophozoite produces by internal gemmation but a single pansporoblast or sporont.

The trophozoites in this order, of whatever type, are generally of amœboid character. Perez has described gregarine-like forms in *Thelohania muenadis*, but their relation to the ordinary forms is uncertain, if indeed they are a stage in the life-cycle of this species at all.

The spore-formation proceeds in a similar manner in the sporont, whether of the type of *Pleistophora* or of *Glugea*. The nucleus divides a certain number of times by binary fission to form daughter-nuclei round which the protoplasm becomes concentrated to form sporoblasts, each of which becomes a spore. According to Perez, however, the whole sporont becomes a single spore in the forms for which he retains the generic name *Nosema* Nägeli, and the same thing may occur exceptionally, according to Stempell, in *Glugea anomala* Moniez. In all other cases, however, the sporont forms more than two sporoblasts and spores, namely, four in *Gurleya*, eight in *Thelohania*, and an indefinite number in *Pleistophora* and *Glugea*. Each sporoblast has at first a single nucleus. It becomes of oval shape, and a tough envelope is secreted round it. Within this the nucleus divides, according to Stempell, into four nuclei, two of which are concerned with the formation of the single relatively very large, polar-capsule, while the other two are the nuclei of the sporoplasm. The spores (Fig. 68) are generally about 3  $\mu$  more or less in length. In *Glugea anomala*, however, the extruded polar filament may be 150  $\mu$  in length.

In the parasites of the type of *Pleistophora* the infected tissue becomes infiltrated with great numbers of sporonts and spores. In the *Glugea*-type the cysts become a mass of spores towards the centre, enclosed by a peripheral zone of protoplasm containing the large vegetative nuclei, the whole surrounded by the cyst-membrane and the connective-tissue capsule. When the growth of the cyst reaches its limit, the vegetative nuclei, according to Stempell, break up into granules of chromatin. Following upon this the whole cyst-wall breaks up, setting free the spores. In this process, however, small spheres of protoplasm may be formed from the peripheral vegetative layer. Each of these spheres contains chromatin-granules derived from the disintegrated vegetative nuclei, which then concentrate themselves to form secondary vegetative nuclei. The spherical

bodies, each with a nucleus thus formed, then wander off into the tissues of the host and form secondary cysts, in which spore-formation proceeds as in the primary cysts.

The infection of fresh hosts always appears to take place by way of the digestive tract, through spores being accidentally swallowed. According to Stempell the polar filament is first extruded, then the envelope dissolves, and the sporoplasm, having gone through a process of binary fission corresponding to its nuclei, emerges as two minute amœbulæ. The two amœbulæ then proceed to conjugate, and the zygote, as a tiny amœbula with a single nucleus, passes through the gut-wall and initiates



FIG. 68.—Spores of various Microsporidia. *a* and *b*, *Plectophoron typanites*; *a*, fresh; *b*, treated with iodine-water to cause the extrusion of the filament; *c* and *d*, *Thelohania octospora*; *c*, fresh; *d*, treated with ether. *e*, *Ichneumon depressa*; *f*, *a. acuta*. From Minchin, after Thelohani, x 1500.

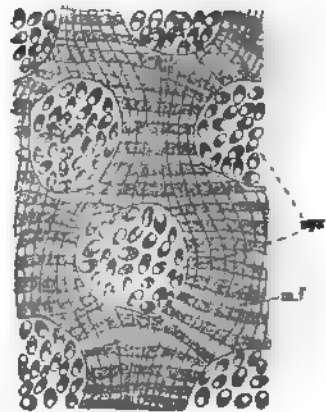


FIG. 69.—Section of muscle-fibre of *C. albicollis* invaded by *Plectophoron typanites* (curley. *m.f.*, muscle-fibrils; *cyst*, cysts of the parasite. From Minchin.

a new parasitic cycle. In *Nosema bombycis* it has long been known that in addition to ordinary casual infection by the digestive tract, hereditary infection also occurs, produced by the penetration of the parasites into the ovary of the silk-worm moth, and the production there of spores which germinate in the newly-hatched caterpillar.

The genera comprised in the Microsporidia may be classified as follows (Perez):—

Section *a*. Polysporogenous. The relatively large trophozoite produces by internal gemination numerous sporonts or pansporoblasts.  
Genera *Glaucis* Thelohani, *Myxocystis* Mrazek.

Section  $\beta$ . Oligosporogenea. The trophozoite becomes a single sporont or pansporoblast. Genera—*Gurleya* Doflein, *Thelohania* Henneguy, and *Pleistophora* Gurley (Fig. 69), characterised by the sporont producing four, eight, or numerous spores respectively.

Section  $\gamma$  Monosporogenea. The trophozoite (sporont) becomes a single spore. Genera—*Nosema* Nageli.

Hitherto the generic names *Glugea* and *Nosema* have been used as synonymous, but, according to Perez, they should be used in the sense given above, the type of the former being *G. anomala* Moniez, of the stickleback, and of the latter *N. bombycis* Nageli, of the silkworm.

Order IV.—*Sarcosporidia*.—The parasites of this order, though of



FIG. 70.—Longitudinal section of a muscle-fibre containing a sarcosporidian parasite. From Muelken, after A. Eschke  $\times 60$ .

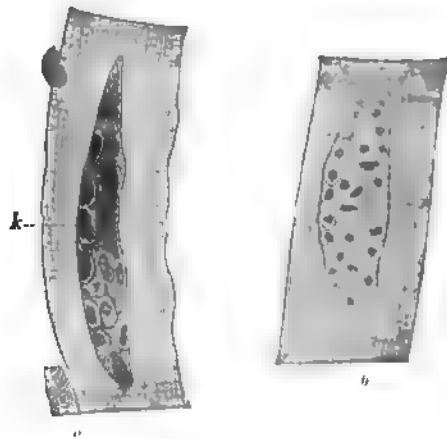


FIG. 71.—*Sarcocystis tenella* in the muscles of the sheep, young stages, already multinucleate. *a*, younger stage, without a striated envelope; *b*, older stage, with striated envelope surrounding an inner membrane. *k*, pansporoblasts. From Muelken, after Bertram.

common occurrence, are the least satisfactorily known of all the principal groups of Sporozoa. They are found as parasites of striped muscles of mammals and birds chiefly, but are known also from reptiles. They are found frequently in domestic animals such as the pig and sheep, and are known also to occur in man (see article "Psorospermiosis"). The striped muscles of the oesophagus or the heart-muscle are the most likely places to find them, but in acute cases all the muscles of the body may be infected by them. The relatively large size of the parasite makes them fairly conspicuous objects when present (Fig. 70).

In its first stage the parasite appears as an elongated whitish body lodged in the substance of a muscle-fibre (Fig. 71 *a*). In this condition it is known as a "Miescher's Tube," a name originally applied to the trophozoites of *Sarcocystis muris* (Blanchard) of the mouse, which have the appearance of white streaks or threads in the muscles. The youngest trophozoites that

have been observed were described by Bertram in *Sarcocystis tenella* of the sheep, and were already multinucleate, but there can be no doubt that in its earliest stage the trophozoite is uninucleate. As the parasite grows, pansporoblasts are formed just as in Myxosporidia or in Microsporidia of the type of *Glugea*, by separation off internally of spheres of protoplasm centred each round a nucleus. At the same time, a striated envelope begins to make its appearance enclosing the whole trophozoite (Fig. 71 b). The exact nature of this envelope is disputed, but its presence is very characteristic of these parasites. It may be compared with the similar

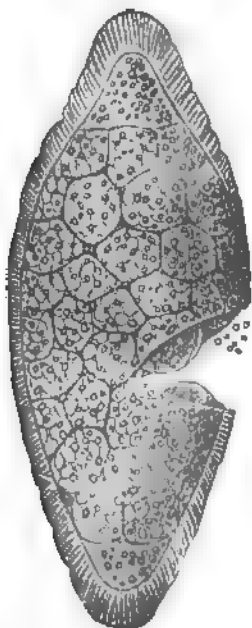


FIG. 72. *Sarcocystis miescheriana* Kuhn from the pig. later stage in which the body has become divided up into numerous chambers or alveoli, each containing numerous spores. From Muchun, after Manz.

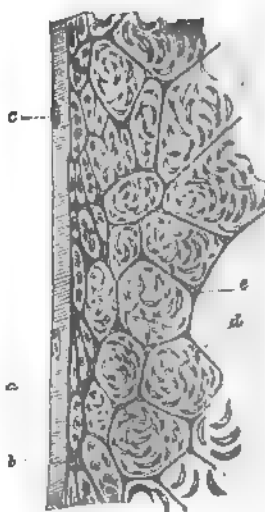


FIG. 73. — *Sarcocystis* of the ox, section of a stage similar to Fig. 72. a, substance of muscle fibre; b, envelope of the parasite; c, nuclei of the muscle; d, spores; e, walls of the alveoli. From Muchun, after v. Eecke.

envelope of *Myxidium lieberkuehnii*, or with the tunica propria of *Glugea anomala*, described above. Extensions inwards of the superficial envelope are also formed, giving the interior of the parasite an alveolar or honey-combed structure. In each alveolus is contained at first a single pansporoblast, which divides up to form numerous spores. Thus, a typical sarcosporidian parasite has immediately under the striated envelope a layer of living protoplasm with nuclei concentrated chiefly at the two poles of the body; internally to this is the zone of spore formation, in which the alveoli contain pansporoblasts dividing up to

form spores (Fig. 73); and towards the centre of the body are found the ripe spores in immense numbers, of which those most centrally placed may, in older parasites, be undergoing disintegration. The parasite grows chiefly in length by forming spores at its two poles.

The Miescher's tube thus constituted may grow until it distends the muscle-fibre greatly beyond its normal width, absorbing the contractile substance as it does so. It then passes out of the muscle-fibre into the adjacent connective tissue of the host. In this second stage the parasite rounds itself off more, and the tissues of the host form a cyst round it. Such cysts may reach a length of 50 mm. in the sheep, and even more than this in other animals. The contents of the cyst consist of vast numbers of spores. By bursting of the cysts their contents become in some cases diffused in the tissues, and the spores are then probably conveyed by the blood to other parts, where they give rise to a fresh infection. Some animals, such as the mouse, are liable to be completely overrun by these parasites, and are killed off by them rapidly, but in most cases *Sarcosporidia* appear to be comparatively harmless to their hosts. Laveran and Mesnil have isolated a toxin, however, which they have named sarcocystine, from the sarcosporidian parasite of sheep.

The statements with regard to the spores are conflicting, but it appears highly probable that they are of two kinds, namely, gymnosporos, which spread the infection in the same host, and true spores, destined to infect fresh hosts. No investigators appear, however, to have found both kinds of spores in the same species of parasite. The gymnosporos are commonly termed "sporozoites" or "Rainey's corpuscles," the latter name being applied more especially to those occurring in the pig. They are sickle-shaped bodies which at a suitable temperature ( $35-37^{\circ}$  C. in the case of *Sarcocystis muris*) shew peculiar movements, a combination of displacement by gliding forwards and of rotation on their long axis. They also exhibit changes of form, and are stated to become amœboid. In *S. muris* they measure about  $12\mu$  in length by  $4\mu$  in breadth, but in other species they may be very much smaller ( $3-4\mu$  in length by  $1\mu$  in breadth).

Bodies which must be regarded as true spores have been described by Laveran and Mesnil from *Sarcocystis tenella* of the sheep (Fig. 74). They are sausage-shaped with one end rounded, the other more attenuated. Near the rounded end is the single large nucleus; the middle portion of the spore is occupied by granular protoplasm; and the more pointed end contains a striated body which perhaps represents a polar capsule. While some investigators have affirmed positively that a polar filament is extruded from the spore, others have been unable to confirm the statement. The existence of a polar capsule in the spores of *Sarcosporidia* is, therefore, at present somewhat doubtful. A noteworthy

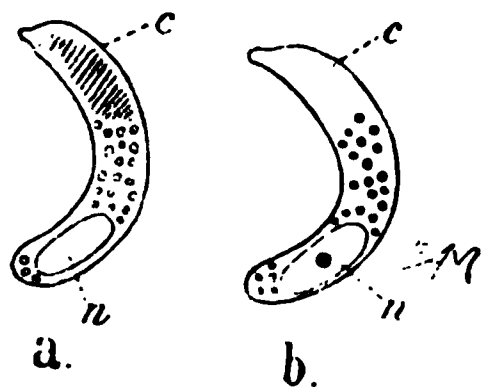


FIG. 74. — Spores of *Sarcocystis tenella* of the sheep: a, in the fresh condition showing a clear nucleus (n), and a striated body (c); b, after staining. From Minchin, after Laveran and Mesnil.



feature of these spores is their delicate nature. Even distilled water deforms them. It is, therefore, very unlikely that they are disseminated simply by being spread abroad like the resistant spores of other Sporozoa.

Nothing whatever is known as to the means by which the infection by Sarcosporidia is brought about. It has been proved by Smith that mice can be infected with *Sarcocystis muris* by feeding them on the flesh of mice already infected. It is very improbable, however, that this represents the natural method of infection even for mice, and cannot do so for many other animals.

All known Sarcosporidia are at present included in a single genus *Sarcocystis* Lankester. Blanchard made two genera *Miescheria* and *Balbiana* to denote forms parasitic in the muscles and in the connective tissue respectively, but since it has been shewn that these two genera represent merely phases in the life-history, they have become obsolete. The best-known species of *Sarcocystis* are *S. muris* Blanchard of the mouse, *S. miescheriana* Kühn of the pig, and *S. tenella* Raillet of the sheep. The last-named species is stated also to occur in man (see article "Psorospermiosis").

Order V.—*Haplosporidia*.—Spores of simple structure, with a single nucleus, and without a polar capsule.

To this order, characterised chiefly by simplicity of structure at all stages and by the absence of the special features distinctive of the three preceding orders, a number of forms have been referred which are parasitic on various invertebrates and on fishes. Quite recently a parasite of man has been added to the list. As in all systematic groups of primitive characters, the precise limits of the group are difficult to define, and the position of many of the forms referred to it is at present somewhat doubtful.

A typical haplosporidian parasite commences its trophic phase as a minute uninucleate corpuscle, in which the nuclei multiply as it grows. The multinucleate trophozoite is commonly spoken of as the plasmodial phase, though it is not, as a rule, amœboid and may have some definite form, in many cases that of a sausage. When it reaches a certain size, the protoplasm becomes divided up to form uninucleate spores. In the simplest cases the spores are rounded or ovoid bodies, without a distinct membrane, and not differentiated for endogenous and exogenous development, but capable of developing in the same or in another host. In other cases the spores may have an elongated, gregarine-like form, as in *Polycaryum*, or may have a definite membrane, as in *Haplosporidium* and its allies. But in all cases alike the spore has a single nucleus, distinct, relatively large, and easily stained, without any other internal differentiation of the spore-contents. This feature distinguishes the parasites of this order at once from Microsporidia, such as *Pleistophora*, to which they often shew considerable resemblance.

The sole human parasite which has been referred to this order is *Rhinosporidium linealyi* Minchin and Fantham (54), which has been found

in tumours of the septum nasi of natives in India. The tumours are vascular, pedunculated growths, resembling a raspberry, which are found in sections to contain great numbers of the parasites imbedded in the connective tissue. The youngest parasites are of irregular form, and consist of granular protoplasm enclosed by a hyaline membrane, and containing apparently numerous minute nuclei. As the parasite grows it becomes generally of spherical form, and its hyaline envelope becomes greatly thickened, forming a definite cyst-wall. Towards the centre of the body the protoplasm becomes segmented into spherical pansporoblasts, each at first uninucleate. In these pansporoblasts the nuclei multiply and give rise to spores, which are formed gradually and successively, the number increasing from one or two to about a dozen. In this way each pansporoblast becomes converted into a spore-morula. Sporulation goes on continually at the expense of the peripheral zone of growing protoplasm, which becomes less apparent as the cyst reaches full size, and is probably used up entirely when the limit of growth is attained. A cyst will then consist of three zones, within the envelope (Fig. 75); at the periphery a zone of uninucleate pansporoblasts; internal to this, an intermediate zone of spore-formation; and most centrally, a great number of spore-morulae. The ripe cysts appear to burst and spread their contents in the tissue of the tumour, thus giving rise to fresh cysts. The tumours recur readily if not completely extirpated. Nothing is known as to the method in which the infection is spread.

The Haplosporidia have been divided by Caullery and Mesnil (15) into three families—*Haplosporidiidae*, *Bertramiidae*, and *Celosporidiidae*—with some additional genera the position of which is doubtful. Among the latter is the genus *Scheriakocella* (Caullery and Mesnil), with a single species parasitic on Crustacea (Cyclops, etc.). This form is remarkable in several points (Fig. 76). The trophozoites are amoeboid and contain a contractile vacuole, the only known instance of the occurrence of such an organ amongst the Sporozoa; the amoebae tend to form plasmodia by fusion; encystment takes place either of single amoebae or of plasmodia, and within the cyst spore-formation proceeds progressively; and the spores themselves, which are of the usual simple type, may multiply by binary fission.

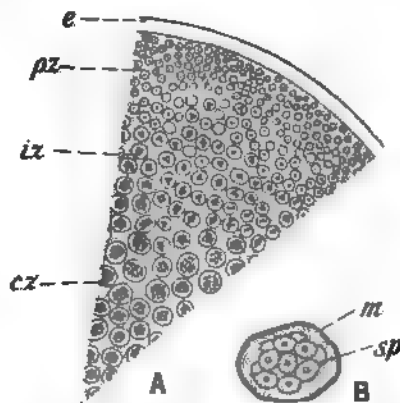


FIG. 75. — *Rhinosporidium lineolus* Minchin and Pantlun. A, segment of a section through a cyst; e, hyaline envelope; pz, peripheral zone of pansporoblasts; ix, intermediate zone of pansporoblasts containing a few spores; cz, central zone of ripe spore-morulae. B, a ripe spore-morula; m, membrane; sp, spores. After Minchin and Pantlun.



thoroughly investigated in all phases of their life-history, they may take a place eventually among the existing orders of Sporozoa, or may rank as representatives of new systematic subdivisions of the class, or may turn out not to belong to the Sporozoa at all, in some cases perhaps not even to the Protozoa. Since it is not possible to give a general account of these aberrant forms, the reader is referred for detailed descriptions of them to Minchin (53) and Cautley and Mesnil (15). A few genera only will be mentioned here, forms either not dealt with in the works mentioned, or important as human parasites.

The genus *Cytoryctes* was founded by Guarnieri in 1892 for the "bodies" observed in deep epithelial cells in vaccine and small-pox pustules. The structures in question were believed to be intracellular parasites belonging to the Protozoa, and were named *Cytoryctes vaccinum* and *C. variolæ* respectively. This interpretation has been criticised or confirmed by subsequent investigators. A summary of the investigations and hypotheses put forward on this subject will be found in the memoir of Councilman, Magrath, and Brinckerhoff (20). Quite recently the etiology of small pox and vaccinia has been the subject of detailed investigations in America by Councilman and other pathologists, in conjunction with whom Calkins (11) has studied the question from the zoological point of view. The results of these concerted investigations, which tend to establish the parasitic and protozoan nature of the bodies in question, are mainly as follows —

In small pox the parasite is found to be confined to lesions of the stained epithelium of the skin and of the mucous membranes of the soft palate, pharynx, and œsophagus, lesions which are regarded as fundamentally specific in character and distribution. The specific lesion of small pox is a focal degeneration of the stratified epithelium which gives rise to the characteristic pock or pustule. The parasites in the lesions are found chiefly in the cells of the rete mucosum up to about the tenth day of the disease, i.e. the sixth day from the appearance of the eruption, rarely later. *Cytoryctes* is to be considered, therefore, as essentially an intracellular parasite of stratified epithelium. It occurs in two forms, a younger cytoplasmic and a later intranuclear form. To these two phases must be added a still earlier but entirely hypothetical phase, covering the period from the primary infection by the air-borne germs (spores) to the first appearance of the parasites in vast numbers in the stratified epithelium; thus making in all, three phases within the human body.

With regard to the first phase of *Cytoryctes*, in the absence of any observations it can only be conjectured that at the seat of the primary infection a process of rapid multiplication takes place, and that from this source minute germs of some kind spread through the body in all directions, probably by means of the blood-current. These germs become lodged in the stratified epithelium of the skin and the commencement of the hecative tract at various points, multiplying there and giving rise to the characteristic eruption. It is possible that this process of primary

multiplication and diffusion of the germs may coincide with the initial fever.

In the second phase the organism appears in the cells of the epithelium in the specific lesions as a minute amœboid organism which reproduces by a process of multiple fission to form minute germs, termed

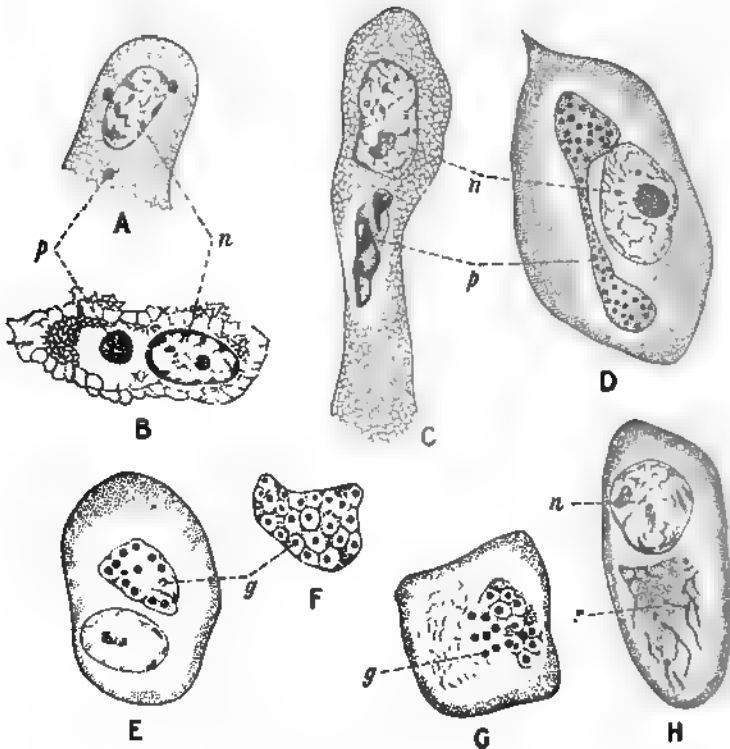


FIG. 77.—*Cytoglyphes variolæ*, "vaccine-cycle." A, epithelial cell containing three parasites at the youngest stage; B, epithelial cell containing an older parasite, shewing commencing differentiation of cytoplasm; C, cell containing an amœboid parasite, nearly full grown, the chromatin, represented black, is distributed in irregular patches; D, a parasite commencing to sporulate within a cell; E, sporulation more advanced, the body of the parasite beginning to divide up; F, sporulation complete, the numerous gemmules lying each in a clear space; G, escape of the gemmules from the parent body; H, remains of a parasite in a cell after the gemmules have been set free from it. *p*, parasite, *n*, nucleus of host-cell, *g*, gemmule, *r*, residual protoplasm of parasite. All the figures except F represent the parasites in the host-cells. After Calkins,  $\times 1300$ .

ly Calkins "gemmules." The parasite may multiply in this way for several generations. In this part of the cycle the parasite is entirely similar to the vaccine-body, and Calkins considers that in vaccinia and variola we have to do with the same organism, which in variola passes through a third intranuclear phase not found, and apparently inhibited, in vaccinia. Hence the second phase is termed the vaccine-cycle (Fig. 77).

The youngest parasites of the vaccine-cycle are minute intracellular

bodies which stain like chromatin and appear to be entirely composed of this substance. They measure about  $7\ \mu$  in diameter, and there may be several in a cell. As the parasite grows, a cytoplasmic portion becomes differentiated, first towards the centre of the body, later at the periphery. In the final stages of growth the parasite is an organism of amoeboid appearance, measuring  $10\text{--}14\ \mu$  in length, consisting of finely granular cytoplasm in which are dispersed irregular patches of chromatin (Fig. 77, C). There is in fact no definite centralised nucleus, but the nuclear substance is scattered in the form of chromidia. When growth is complete the chromatin becomes broken up into minute granules diffused evenly through the cytoplasm of the parasite (Fig. 77, D). These granules become more definite and form the gemmules. Each comes to lie in a minute vesicle or clear space in the cytoplasm (Fig. 77, F). Finally the gemmules are set free, and infect fresh cells, where they are found in the form of the youngest stages already described. After setting free the gemmules, the body of the parasite remains as a residual mass of protoplasm containing a few fragments of chromatin (Fig. 77, H). The residuum ultimately disintegrates.

The third or intranuclear phase of the parasite (Fig. 78), specially characteristic of small-pox, is initiated by gemmules, formed in the manner described in the preceding paragraph, passing into the interior of the host cell (Fig. 78, A). In this situation they develop into amoeboid bodies containing chromatin scattered irregularly in their cytoplasm (Fig. 78, B, C). According to Calkins the intranuclear parasites become gametocytes of two kinds, but considerable doubt must attach to this part of the life cycle. The supposed male forms are spherical, at first with central chromatin from which a ring of minute chromatin dots is formed at the periphery of the body (Fig. 78, D). These chromatin dots are interpreted as the almost ultramicroscopical male gametes, which become liberated, leaving the rest of the body as a residuum. The female gametocytes are spherical with central chromatin (Fig. 78, E). Each is believed to become a female gamete, and to be fertilised by a male gamete, after which the parasite is to be termed the zygote, a fairly large more or less amoeboid body with a central mass of chromatin. The zygote pushes the chromatin of the host nucleus to one side, and ultimately absorbs it. The chromatin of the zygote next becomes distributed through the body of the parasite by fragmentation, and the fragments, at first minute, grow in size (Fig. 78, F). At this stage the parasite breaks out of the host-nucleus, the membrane of which becomes disintegrated. Each chromatin-mass of the parasite becomes a body which, as it is destined to form several spores, should be called a pansporoblast. (Calkins, however, uses the term pansporoblast for the whole zygote, and proposes for the masses of chromatin which produce such a number of spores, but the word sporoblast should always be used to denote the body from which a single spore arises.) Each pansporoblast (in our sense, becomes a hollow ring or sphere of chromatin, from which the spores are differentiated (Fig. 78, G, H). The spore is a minute body,

the bulk of which is a refringent vacuole, bearing at one pole a clump of chromatin. The spores may develop within the nucleus into secondary pansporoblasts, from which spores are formed again by a process of

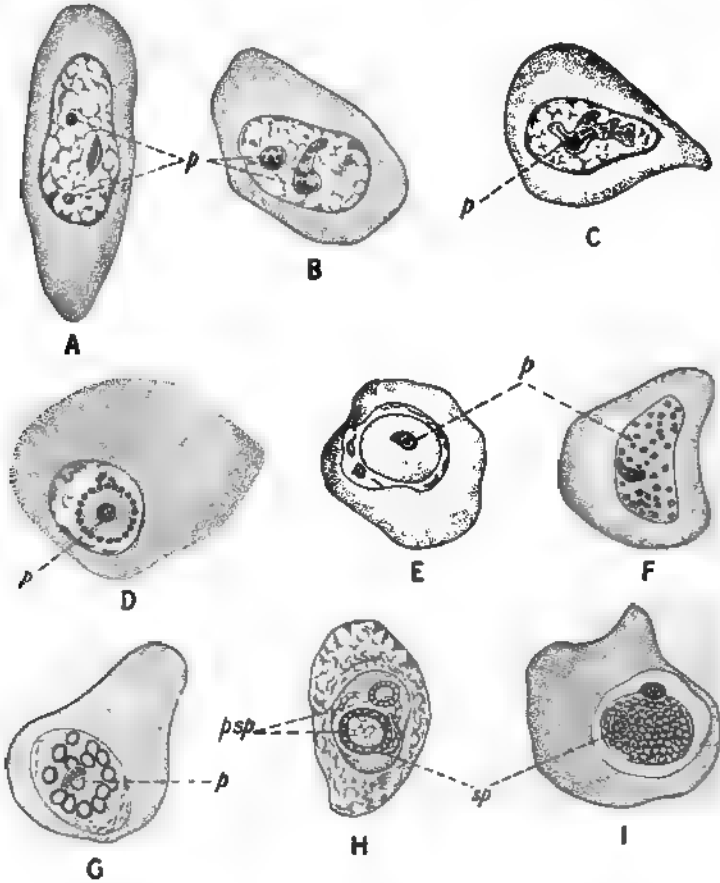


FIG. 78.—*Cytospora variator*, intranuclear cycle in epithelial cells. A, a cell containing two young parasites lodged in the nucleus; B, similar cell containing two older parasites; C, nearly full-grown umbeloid parasite in the nucleus of the cell; D, supposed male gametocyte, with chromatin granules at the periphery, the host-nucleus nearly absorbed; E, supposed female gamete or zygote; F, the zygote commencing to sporulate, containing numerous small masses of chromatin and a residual mass, the host-nucleus quite absorbed; G, the small chromatin-masses of the preceding stage have the form of rings or hollow spheres (pansporoblasts); H, differentiation of spores from chromatin-rings of the preceding stage; I, parasite containing a mass of ripe spores. *psp*, pansporoblasts; *sp*, spores; other letters as in Fig. 77. After Calkins,  $\times 1500$ .

schizogony in the same manner as in the primary pansporoblasts. These minute refringent spores are probably the means by which the infection is spread.

Calkins considers that *Cytospora* should be classed with the Micro-



sporidia, but since the spores do not apparently contain any polar filament, and are uninucleate, it is rather with the Haplosporidia that the parasite should be classed. In this group it resembles most the peculiar parasite of brook-trout described by Calkins under the name *Lymphosporidium*. Calkins puts together, as a family *Cytoryctidae*, the genera *Cytoryctes* Guarnieri, *Lymphosporidium* C. and *Caryoryctes* C., the last being a peculiar intranuclear parasite of *Paramecium* very similar in many points to the third phase of the small-pox parasite. In the power of multiplication by fission within the host possessed by the spores, the life-cycle of *Cytoryctes* resembles that of *Scheviukovella* (see p. 107).

In the foregoing paragraphs the life-cycle of *Cytoryctes* has been sketched in its principal outlines, following the description of the American investigators. Siegel (80), on the other hand, gives a totally different account of this parasite, altering even the spelling of the name to *Cytorhyctes*. Siegel finds several species of this organism to be the cause of different acute exanthemata of man and animals; such are *Cytorhyctes vacciniæ* Guarnieri of small-pox, *C. aphtharum* S. of foot-and-mouth disease, *C. scarlatinae* S. of scarlet fever, and *C. luis* S. of syphilis. The parasites occur under two forms. The first is a mobile form, .5 to 1  $\mu$  in length by .1  $\mu$  in breadth. The body is pear-shaped, with one end running out into a delicate refringent process, which is apparently of the nature of a flagellum, but can be protruded and retracted. By means of this organ the parasite performs movements which are described as being very similar to those of *Trypanoplasma*, and consist of locomotion round a circle of about 15  $\mu$  in diameter. The protoplasmic body of the parasite contains two masses of chromatin, one situated at the pointed end, the other at the broad end. The mobile forms may multiply by binary fission, or by sporulation following multiple division of the nucleus. As the result of the latter process they may break up into mobile forms again or into individuals of the second or non-mobile type which are termed cystospores and probably represent the infective, resistant phase. The cystospores (in *C. vacciniæ*) are larger than the mobile forms and divide each into two sporozoites. These parasites are found in the blood or expressed juices of the organs, and are able to pass through a Chamberland filter. The different species may shew characteristic differences of parasitic habitat. *C. aphtharum* attacks the nuclei of the epithelial cells. *C. luis* sporulates in the connective tissue and in the blood-vessels, never in the epithelium.

Siegel regards the genus *Cytorhyctes* as one intermediate between Sporozoa and Flagellata. It is difficult to reconcile his results with those of the American investigators, though the mobile forms described by Siegel might possibly represent a phase of the parasite described by Calkins. Siegel's criticism that the parasites described by the Americans were seen in material prepared from corpses, is met by Magrath and Brinckerhoff's discovery of the same forms in monkeys artificially inoculated. It may be also pointed out that the claims of *Cytorhyctes luis* to be the cause of syphilis conflict with those of *Treponema pallidum* described on



p. 46. Maclellan suggests that *Cytorhyctes luis* represents one stage, and *Treponema pallidum* another, of the life-cycle of the same organism.

Prowazek (69) has recently published the results of a critical examination into the nature of the vaccine virus. He comes to conclusions similar to those of Foa (25), namely that Guarnieri's bodies, though specific for vaccine, are not the parasites, since if injured or destroyed by the actions of reagents, such as salt solution or trypsin, infection can still be carried out successfully with the lymph. He denies also that the bodies shew any developmental cycle, and, from micro-chemical and staining reactions, concludes that they are chromidia, i.e. extra-nuclear chromatin of the host-cells. In view of these conflicting statements, the nature of the parasites of vaccine and variola must be considered at present entirely problematical.<sup>1</sup>

*Coccilioides immitis* and *C. pyogenes* are the names given by Rixford and Gilchrist to bodies believed to be protozoa observed in certain contagious skin-diseases (see article "Psorospermiosis"). A description of the parasites and a discussion of their affinities will be found in Blanchard (3). *Lymphocystis johnstonei* Woodcock (87), a parasite of plaice and flounders, is interesting on account of its resemblance to gregarines, not known to occur otherwise in vertebrate hosts.

Finally there remain for mention the alleged parasites of cancer, so often described under many forms and synonyms. It is not possible within the limits of this article to give a detailed account of the structures that have been identified as parasites of cancer, or to discuss the systematic position to which they have been referred by different authors. To perhaps the majority of investigators the very existence of a cancer-parasite is extremely dubious. It is sufficient here merely to refer to the latest identification of this elusive organism, under the name *Histoplasidium carcinomatosum*, by Feinberg. This author has recently published a ponderous tome, which I have not been able to see, and in which a complete life-history of the parasite, both within and without the human body, is stated to have been worked out.

**Class IV.—Infusoria.**—Protozoa in which the organs of locomotion are cilia, and in which the nuclear apparatus is differentiated into a vegetative macronucleus and a generative micronucleus.

The term Infusoria had originally an application more extensive than its current use, being employed to denote any minute animalcules that make their appearance in infusions, such as Flagellata or Rotifers. Hence in modern works the class at present under consideration is denoted by the term Ciliophora, expressive, by a hybrid etymology, of the chief peculiarity of the class.

The Infusoria fall naturally into two subclasses, the Ciliata and the Suctorina (Acinetaria). In the Ciliata the cilia are retained throughout the active life of the animal, and only disappear temporarily during the

<sup>1</sup> The micro-organism of vaccine has also been named *Strombodes jenneri* by Sjöbring in a memoir which I have not seen (*Hygiea*, Stockholm, n.f. ii. 1. 1902).

encysted phase. In the Suctoria, on the other hand, the cilia are only present in an early larval stage of the life-history, and disappear completely in the adult condition, in which the function of the capture of food is undertaken by peculiar suckers and tentacles. Some Suctoria are endoparasites of other Protozoa during the larval phase, but none of them are known as internal parasites of Metazoa. For further information concerning the Suctoria, the reader is therefore referred to general treatises on Protozoa.

The Ciliata exhibit a more complex type of organisation and reproduction than any other protozoa. Examples of this group are among the most familiar of microscopic organisms, and will be found described in any elementary text-book of zoology. The body is typically ovoid or barrel-shaped, one pole being directed forwards in swimming; in creeping forms the body is flattened, so that a ventral surface, on which the mouth is situated, can be distinguished from a dorsal surface. In fixed forms the animal is attached by the pole opposite to the mouth, and the point of fixation may be drawn out as in *Vorticella*, into a long, contractile stalk, or the body may be sessile.

The characteristic cilia shew variations in their arrangement which are distinctive of the several orders into which the subclass is divided, and will be described below. The most primitive type of these organs is seen in the swimming forms, as minute hair-like extensions of the superficial layer of the body-protoplasm, arranged in rows to form a fur-like covering to the body, but the primitive simple arrangement of the rows of cilia becomes modified in various ways. The first specialisation of the ciliary apparatus is the acquisition of an adoral or peristomial zone of larger cilia, specialised for the capture of food by causing water currents towards the mouth, while the cilia of the general body-covering remain purely locomotor in function. The locomotor cilia may be reduced in number and specialised in arrangement, or in fixed forms may be absent altogether. In addition to cilia of the primitive type, other organs may be present which are probably derived from them, such as the cirri and the membranellæ.

The body of a Ciliate Infusorian is enclosed by a cuticle or *pellicle*, which may be very thin, or may be greatly thickened to form a jointed armour or *lorica* as in *Coleps*. The pellicle is, with rare exceptions, interrupted at one point by a definite cell-mouth or *cystostome* for the ingestion of food. The fæcal substances are rejected by a pore which is probably also constant in position, though, as a rule, only visible when in use; but in some cases there is a definite cell-anus or *cytopyge*, recognisable at all times. The mouth is primitively a slit or pore which forms a passage through the ectoplasm, and which may be capable of being closed, or may remain permanently open; in the latter case there may be special arrangements for keeping the aperture distended. The mouth may remain at the surface of the body, or may be carried inwards by a funnel-shaped depression of the ectoplasm, whereby a vestibule or œsophagus is formed as a tube leading to the true mouth. In this vestibule arise the special adoral differentiations of the cilia already mentioned.

Internal to the pellicle the body is always divisible into ectoplasm and endoplasm, sometimes termed cortex and medulla in this class of Protozoa. The ectoplasm, of which the pellicle is to be reckoned as the outermost portion, is typically composed of an external alveolar layer and an internal excretory layer. From the alveolar layer arise the cilia, piercing the pellicle to pass to the exterior. Below each row of cilia contractile fibres or myonemes are found running in a longitudinal direction. In many Ciliata the alveolar layer also contains minute spindle-shaped bodies called trichocysts, probably defensive or offensive in nature, from which on stimulation a delicate thread can be shot out. The lower or excretory layer of the ectoplasm contains a system of channels from which the contractile vacuoles are fed. One or several contractile vacuoles may be present.

The endoplasm or medulla is far more fluid in nature than the ectoplasm, and exhibits movements of rotation during life. It lodges the food-vacuoles, granulations of various kinds, and the two nuclei. The macronucleus is a conspicuous structure usually of compact, more or less oval form, but is subject to the greatest possible variation, being single or multiple, sometimes even in a condition of fragmentation, and, when single, it may be drawn out to be sausage-shaped, or moniliform. The micronucleus is usually single, occasionally, however, multiple, and appears during the vegetative life of the animal as a minute refringent body which stains with difficulty, and is easily overlooked.

The reproduction of Ciliata takes place in the active condition by fission or gemmation, and in the encysted condition by sporulation. Binary fission is typically transverse to the morphologically longitudinal axis of the body. It is preceded by doubling of the contractile vacuoles, and division of the two nuclei. The micronucleus divides by a simple form of mitosis, the macronucleus by the direct method.

Encystment frequently takes place in Ciliata as a protection against desiccation or other unfavourable conditions. Parasitic forms are able in this manner to pass out of the host, and remain dormant until taken up by a fresh host. Within the cyst the animal may remain without multiplication until in favourable circumstances it is able to become free from the cyst and to recommence an active existence, after having renewed its locomotor apparatus temporarily lost. Or the encysted animal may by a process of multiple fission give rise to a number of minute individuals, which, under suitable conditions, are set free and develop each into an individual of the ordinary type.

Many observations and experiments shew that this process of vegetative reproduction cannot continue indefinitely, but leads after a time to signs of senility and degeneration in the animalcules, requiring a renewal of the vital powers which is given, apparently, by the process of sexual fertilisation. In correlation with the highly complex organisation of the Infusoria, the process of conjugation is also extremely complicated, and subject to great variation in detail.

The process of events is essentially as follows in all cases :—

- (1) Degeneration and ultimate absorption of the macronucleus.
- (2) Division of the micronucleus of each gamete to form a certain number of daughter-nuclei, typically four, which are all absorbed except one.
- (3) Division of the single remaining daughter-micronucleus into two pronuclei, which may be distinguished as the active and passive pronuclei.
- (4) Migration of the active pronucleus of each gamete across into the body of the other gamete, if the gametes remain distinct, to fuse with the passive pronucleus of the other gamete. If the

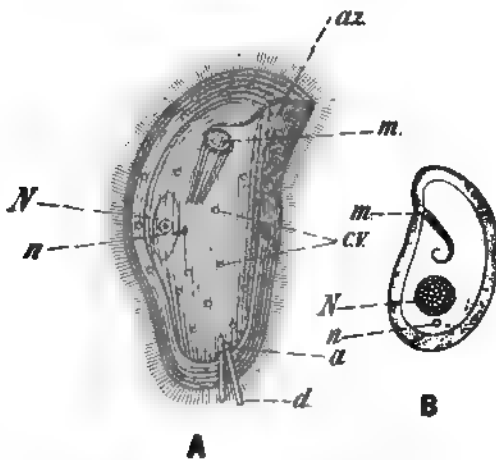


FIG. 79.—A, *Chilodon cucullulus*, B, *Chilodon dentatus*, drawn in outline only. m, mouth, supported by an apparatus of rods; az, adoral zone of cilia, not specially enlarged; c.v., the numerous contractile vacuoles; N, macronucleus; n, micronucleus; d, anus from which the shells of two distomes, d. are being extended. From Bütschli, A, after Stein, B, after Gruber.

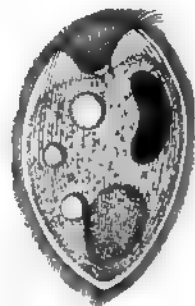


FIG. 80. *Balantidium coli*, showing nucleus (on the right), vacuoles (on the left), peristome (placed uppermost), and a mass of food ingested (towards the lower end of the figure). After Leuckart, from Braun.

gametes have fused, the same process goes on within the body of the zygote.

- (5) Division of each synkaryon into two sister-nuclei, one of which increases rapidly in size to form a new macronucleus, taking the place of the old one, while the other remains small, and becomes a micronucleus.

Reproduction results therefore in the complete renewal of the nuclear apparatus of the gametes, each being provided finally with a pair of dissimilar nuclei derived entirely from the synkaryon. Each individual then starts a fresh cycle of vegetative activity, and fission is sometimes so rapid immediately after conjugation that its products are small individuals, which grow to the normal size of the species. From the facts it may be inferred that the macronucleus of Infusoria is vegetative in function, regulating the activity and metabolism of the individual cell-body, and

tending in consequence to become worn out and effete; but that the micronucleus consists of generative chromatin held in reserve for the process of conjugation, after which it gives off material which becomes the vegetative chromatin of a fresh cycle of generations, taking the place of that which had become effete.

Among the Ciliata an entozoic habitat is fairly common. They are found chiefly in the digestive tracts of their hosts, sometimes in other internal cavities, but never as tissue-parasites. The Ciliata include four orders:—

(1) Order *Holotricha*. The cilia are approximately of equal length and thickness all over the body, without any special adoral zone of enlarged cilia.

Familiar examples are the common *Paramecium* and the parasitic

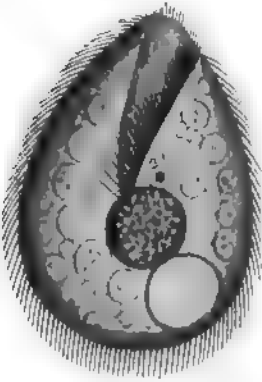


FIG. 81.—*Balantidium minimum* Schaud. showing nucleus, contractile vacuole, and food-vacuoles in the endoplasm. After Schaudinn, from Braun.

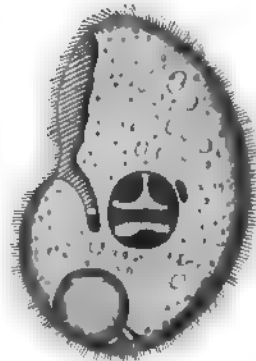


FIG. 82.—*Nyctotherus fava* Schaud. From life. After Schaudinn, from Braun.

genus *Opalina* already mentioned. Two species belonging to this order have been described from the human intestine, *Chilodon dentatus* (Duj.) (Fig. 79) and *Colpoda cucullus* (vide Gniart [27]).

(2) Order *Heterotricha*. A special adoral zone of larger cilia is always present.

Genera belonging to this order are found very commonly occurring as parasites in the intestines of various animals. Two genera are known which include species parasitic in man, namely, the genera *Balantidium* and *Nyctotherus*.

The genus *Balantidium* is characterised by an oval body with the peristome starting from near the anterior end, where it is broadest, becoming narrower as it passes backwards on the side of the body; at the opposite pole of the body is the anus. The nucleus is compact, oval, or almost sausage-shaped, with a single micronucleus close to it. *B. coli* (Malnisten) occurs commonly in the rectum of the pig, occasionally in

the colon of man (Fig. 80). A second species, *B. minutum* Schaudinn, has also been described from man (Fig. 81).

The genus *Nyctotherus* has the body bean-shaped, with the large peristome on the concave side, and extending from the anterior end to about the middle of the body, at which point the long, curved œsophagus arises and passes into the body. The macronucleus is compact and oval in form, with a single micronucleus situated close to it. The single contractile vacuole is at the posterior end of the body, close to a distinct anal tube opening at the posterior pole. Species of this genus are found parasitic in the cockroach and the frog, and can nearly always be found in the digestive tracts of these animals. A single species, *N. faba* Schaud. has been described from the digestive tract of man (Fig. 82).

(3) Order *Hypotricha*.—Ciliata of creeping habit, with well-marked dorsal and ventral surfaces, and usually with cirri in addition to, or without, ordinary cilia. The common *Stylonychia* is a well-known example of this order, which contains no forms occurring as internal parasites.

(4) Order *Peritricha*.—Ciliata generally of fixed habit, hence without locomotor cilia, which, if present, take the form of a ring, present permanently or developed temporarily, near the aboral end of the body. Apart from this ring the body has no cilia other than the adoral spiral zone. The familiar *Vorticella* may be cited as a characteristic example of the order, which contains no forms of entozoic habit.

E. A. MINCHIN.

## REFERENCES

The following list of references does not pretend to be a complete bibliography of the Protozoa, but to indicate (1) works of general and comprehensive nature dealing with Protozoa, or with a particular group of Protozoa, and containing exhaustive bibliographies; such works are marked with an asterisk; (2) recent memoirs cited in the text.

The following abbreviations of the titles of periodicals are used: *A.K.G.A.* (*Arbeiten aus dem Kaiserlichen Gesundheitsamte*, Berlin); *A.P.K.* (*Archiv für Protistenkunde*, Jena); *C.R.S.B.* (*Comptes Rendus de la Société de Biologie*, Paris); *J.H.* (*Journal of Hygiene*, Cambridge); *Q.J.M.S.* (*Quarterly Journal of Microscopical Science*, London); *S.M.I.* (*Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India*, Calcutta).

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E. A. M.

## MOSQUITOES OR CULICIDÆ

By FRED. V. THEOBALD, M.A.

OF all blood-sucking insects the mosquitoes are the most important, not only because their bites are a constant source of annoyance in all climates, but because the part they play in the spread of certain diseases is most inimical to man. Any mosquito may carry blood organisms or poisons, and thus their bites may prove not only irritating but dangerous to the bitten person. It is, however, their share in the diffusion of certain definite diseases that makes them of such vital medical interest. These insects not only carry the germs of disease, but constitute the host in which the germs pass part of their life-cycle, so that without the mosquito those parasites could not exist. For this reason the most exact and extensive knowledge concerning the life-history, habits, and structure of these flies is essential. The diseases in which mosquitoes play a prominent part are the malarial fevers, yellow fever, filariasis, dengue, and possibly others. In the case of yellow fever, in which the organism is uncertain, it is not at present known that the mosquito-carrier acts in any way as the host of the parasite, but this has been conclusively proved to be true as regards malaria and filariasis by Ross, Grassi, Manson, Bancroft, and others. To understand and study the life-histories of these disease-producing parasites, a working knowledge of the internal anatomy of the mosquito is therefore necessary.

Only certain species are at present known to carry definite diseases. For instance, yellow fever is carried only by the tiger mosquito, *Stegomyia fasciata* Fabricius; filariæ by *Culex fatigans* Wiedemann, and possibly by *Myzomyia rossii* Giles and others. On the other hand, malaria is distributed by many species which all belong to one particular group of these insects called Anophelinae.

Mosquitoes belong to a family of Diptera or two-winged flies called CULICIDÆ. The Culicidæ can be told at once from all other Diptera by the following characters, which are important, since many other insects, that have no possible bearing on the diseases spread by mosquitoes, are often confused with the Culicidæ.

**Characters of the Culicidæ.**—The body of the mosquito, as in other

Hexapods (erroneously called insects), is divided into three regions:—(i.) the head, (ii.) the thorax, and (iii.) the abdomen.

The head has the mouth-parts drawn out into a long piercing proboscis, often as long as or even longer than the whole body. The head, thorax, and abdomen, as a rule, are clothed with distinct scales (all Culicines and Aedines), but these may only occur on the head (*Anopheles* sen. st.), the thorax and abdomen being hairy. The wings have normally six longitudinal veins (Anophelines, Culicines, etc.), but in one group they have seven (Heptaphlebomyines); all have two distinct fork-cells, and the veins in all true Culicidæ have definite shaped scales along them; the so-called costal vein—the vein along the outer edge of the wing—passes completely around the wing and carries scales, which form a more or less pronounced fringe. Mosquitoes undergo a complete metamorphosis, that is, there is an active, growing, feeding stage—the larva; a non-growing, non-feeding stage—the pupa, during which stage the larva is transformed into the active, flying, sexual adult—the mosquito. In all known Culicidæ the larval and pupal stages are passed in water or very damp mud, and it is quite unlikely that any will be found to be other than aquatic in their immature stages.

**The External Structure of a Typical Mosquito** (Fig. 85).—The three main areas, (i.) the head, (ii.) the thorax, and (iii.) the abdomen, into which the mosquito is divided, are sharply separated from one another. The head varies in its general form in the different groups, but can be reduced to a simple type. On each side there is a large compound eye (Fig. 85, *D*), which occupies a greater area in the males than in the females. The eyes are frequently of a beautiful colour in life, but fade, as a rule, in dried specimens; there are no very important characters to be noticed in these typical hexapod organs. The space between the eyes above is called the occiput, and that between them in front the vertex; the sides of the head the genæ, the back the nape or neck; the front of the head between the eyes is called the frons, which in certain genera (*Runchomyia*) may project as a prominence. The head is covered more or less completely with scales and bristles or chætæ. Projecting forward from the head is a blunt process—the clypeus (*C*). This may be simple (*Culex*) or may be ridged with lateral processes (*Quasistegomyia*, etc.); it may be nude (*Anopheles*, *Culex*, etc.), or hairy (*Joblotia*), or with scales (*Stegomyia*). The mouth is prolonged into a long sucking and piercing tube called the proboscis (*A*), which is straight in most genera (*Culex*, *Anophelines*, *Stegomyia*, etc.), or much curved (*Megarhinus*, *Toxorhynchites*), or elbowed (*Limatus*). The proboscis may be shorter (*Uranotænia*) or longer (*Dendromyia*) than the body, and may be acuminate (*Culex*) or swollen apically (*Uranotænia*). The mouth-parts (Fig. 83) constituting the proboscis are as follows:—the labrum, epipharynx, or upper lip (*H*); two sharp lancet-like needles—the mandibles; two pointed maxillæ; a single flattened process—the hypopharynx (*B*); and the large gutter-shaped lower lip or labium which ends in two jointed processes—the labella (*E*). The labium is fleshy, covered with scales outside and

deeply grooved inside, and when at rest the groove contains the piercing mouth-parts. Closing in the groove above is the labrum, with the epipharynx, with which it is fused, as seen in the section (Fig. 84); this is deeply grooved. Beneath it lies the hypopharynx, which is flat, and forms

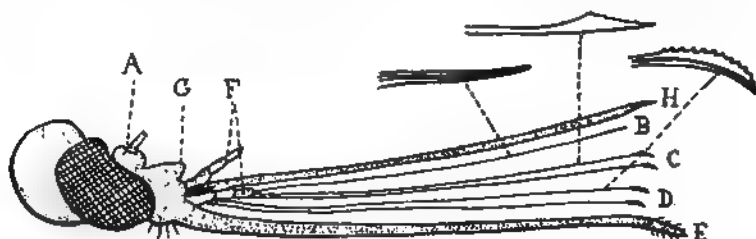


FIG. 83.—Head of *Culex*. A, antenna; G, clypeus; F, palpi. H, upper lip; B, hypopharynx; C, mandibles; D, maxillae; E, lower lip.

with the labrum the tube by which the blood is drawn into the mosquito's body; the hypopharynx is perforated by the salivary duct, and down this tube the saliva is ejected into the wound caused by the insect. The mandibles and maxillae are thin, sharp, chitinous rods; the latter usually have the terminal cutting-edge serrated. The fleshy labium acts as a protecting organ to these more delicate mouth-parts, all of which penetrate the skin in the act of feeding, whilst the labium remains outside, the piercing organs passing between the bent labella. The whole labium bends on itself as the other organs enter the flesh, and to some extent guides them during the process. In the male the mandibles and maxillae are very rudimentary, hence the male mosquitoes do not bite as a rule.

There is considerable modification in the minute structure of these mouth-parts in the different groups.

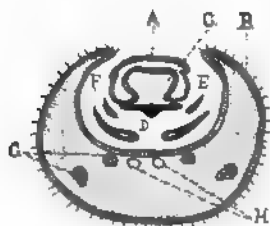


FIG. 84. Section of proboscis. A, upper lip; B, lower lip; C, hypopharynx; D, duct; E, mandibles; F, maxillae; H, tracheae; G, extensor and flexor muscles. After Nuttall and Shipley.

Closely attached to the mouth are the palps or sensory organs (Fig. 83, F, and Fig. 85, B), by the characters of which the groups of Culicidae have in the past been separated. These organs are composed of two or more segments. In some instances they are very short (*Aedinae*) in the female and male, in others they are long in both sexes (*Anophelinae*, *Megarhinus*), while in others they are long in the males but short in the females (*Culex*). They may be as

long as the proboscis in the females (*Anopheles*), half as long (*Runchomyia*), or scarcely perceptible (*Urautania*). In the males when long they may excel the proboscis in length (*Culex*, *Megarhinus*, etc.), and may be acuminate or clubbed (*Anophelinae*, *Theobaldia*). The greatest number of segments seems to be six. The palps vary greatly in size and shape in closely allied groups, and so

be taken as valid characters of higher value than for separating

(Note the long palps in the female *Megarhinus* and the short the closely allied *Toxorhynchites*.) The *antennæ* (Fig. 83, *A*, and *P*), the remaining structures to be noticed on the head, are com-

posed of a large basal segment and a long flagellum made up of many segments. In the female segments are provided with short hairs arranged in rows, in the males the *antennæ* are usually shorter, the verticillate segments being long (*Culex*, *Aedes*, *Stegomyia*), but may be only pilose in the female (*Sabethes*, *Aedes*, *Wyeomyia*).

In certain genera the basal segments of the *antennæ* are modified, being long and thin (e.g., *Culex*), others short and thick and scaly (*Megarhinus*); in one group the basal hairs of one segment become modified into a comb-like organ (*Lophomyia*).

The *thorax* forms a middle area between the head and the abdomen. The major portion is composed of the mid-thorax or prothorax (*F*), which at the anterior end always has a small

restricted piece—the *prothoracic lobe* (*E*)—present in the *Anophelinae* a rounded posterior lobe whilst in the other

it is distinctly trilobed. The prothorax is represented by two processes called the prothoracic lobes (*E*). The hind part or metathorax (*I*) is rounded and placed under the scutellum; at the sides are the pleuræ, which are, however, of little diagnostic value.

All parts of the thorax may be covered with scales; as a rule the metathorax is nude (*Metanotopsilæ*) (Fig. 97, *C*), but it may carry scales and chætæ (*Metanototrichæ*) (Fig. 97, *A* and *B*).

The organs of locomotion (wings and legs) are attached to the thorax,

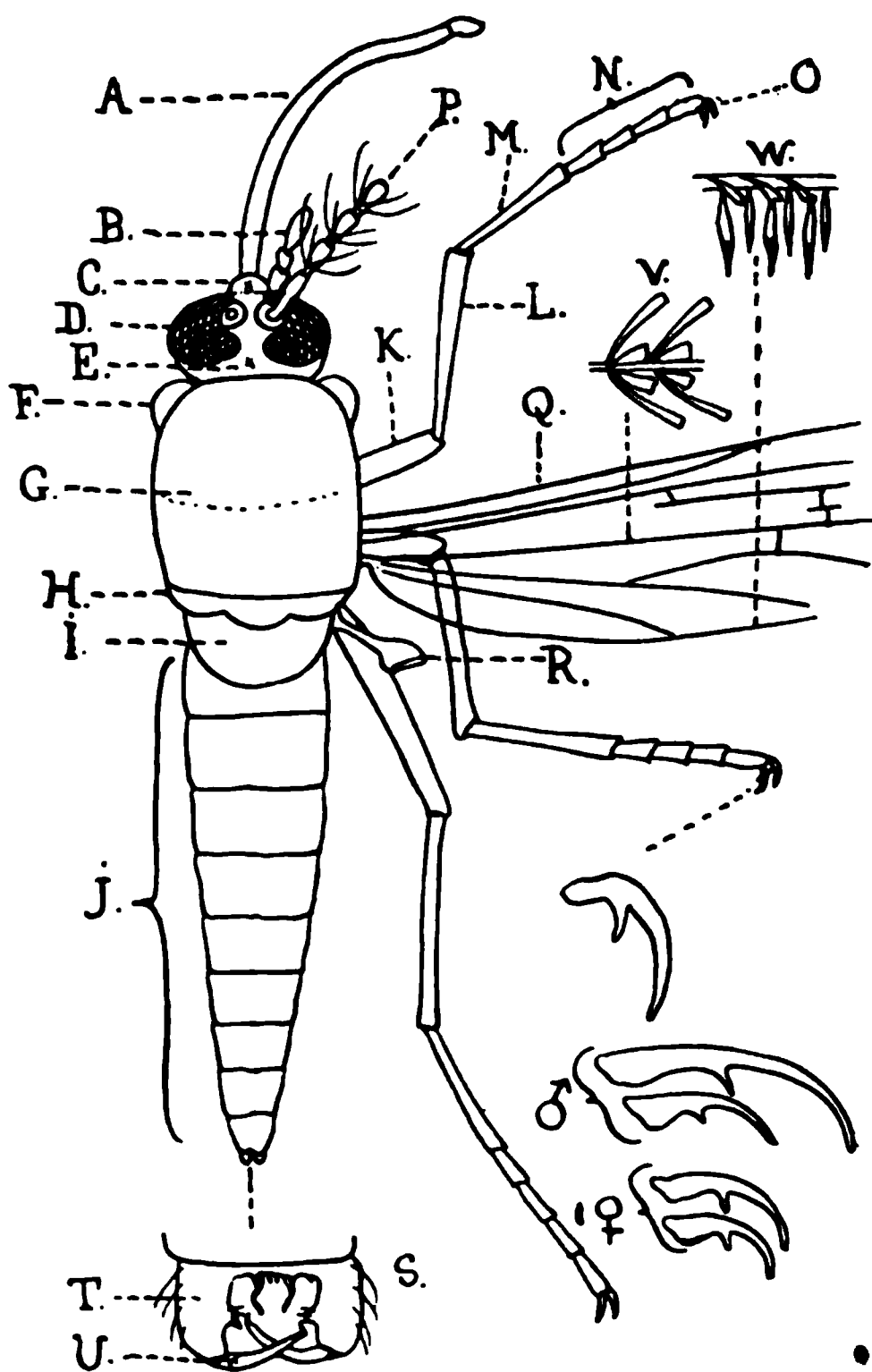


FIG. 85.—Structure of a typical mosquito. *A*, proboscis; *B*, palpus; *C*, clypeus; *D*, eye; *E*, occiput; *F*, prothoracic lobe; *G*, mesothorax; *H*, scutellum; *I*, metathorax; *J*, abdomen; *K*, femur; *L*, tibia; *M*, metatarsus; *N*, tarsus; *O*, unguis; *P*, antenna; *Q*, wing; *R*, halter; *S*, male genitalia; *T*, basal lobe of genitalia; *U*, clasper; *V*, vein-scales; *W*, fringe-scales; *X* and *Y*, unguis.

the wings to the upper portion, the legs to the sides of the pleuræ. Culicidæ, in common with all Diptera, have two wings arising from the side of the mesonotum towards its posterior end, while attached to the metathorax at its base are the pair of club-shaped processes, the balancers, poisers, or halteres, which are remnants of the second pair of wings.

The venation of the wing is shewn in Fig. 86. The costal vein runs around the whole border of the wing; there are six longitudinal veins in all but the Heptaphlebomyinæ, in which there are seven. Beneath the upper costal border, arising from the root of the wing, is the subcostal vein, which joins the costal before the tip of the wing; beneath it comes the first longitudinal vein, which ends near the tip of the wing. The second long vein arises from the first, and ends in two branches which form the so-called first submarginal cell (the first fork-cell). The third long vein is simple, and arises at or near the junction of two cross-veins, the supernumerary and the mid. The fourth arises from the base of the

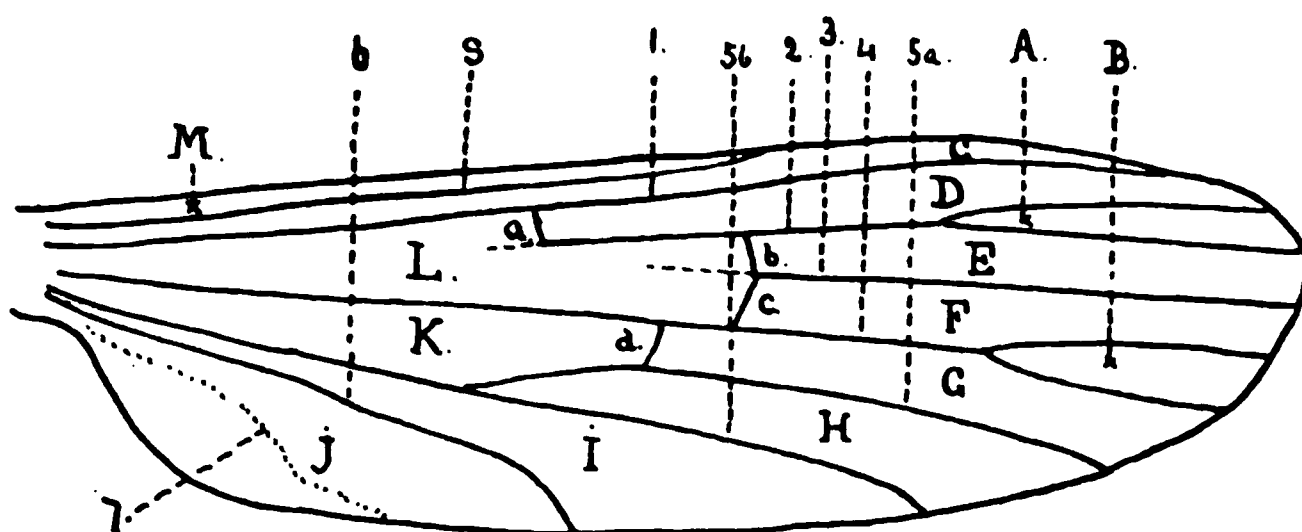


FIG. 86.—Wing of *Culex*. 1 to 6, first to sixth longitudinal veins; 5a and 5b, upper and lower branches of fifth vein; A, first submarginal cell; B, second posterior cell; C, subcostal cell; D, marginal cell; E, second submarginal cell; F, first posterior cell; G, third posterior cell; H, anal cell; I, auxiliary cell; J, spurious cell; K, second basal cell; L, first basal cell; M, costal cell; a, marginal cross-vein; b, supernumerary cross-vein; c, mid cross-vein; d, posterior cross-vein.

wing, and terminates in two branches which form the second posterior cell (second fork-cell). The fifth also arises from the base of the wing, and sends off a branch about or shortly after half its length. The sixth and seventh both arise from the base of the wing, and are both simple. The remaining parts of the wing, the cell-areas, etc., are named in Fig. 86.

The legs are attached to the pro-, meso-, and meta-thorax rings on the lower part of the pleuræ. Each leg consists of nine segments. The basal one, by means of which they are attached to the body, is called the coxa; then follows a small segment, the trochanter, which is succeeded by the large femur, then the shank or tibia, and the foot, made up of five segments, the basal one of which is usually much the longest and known as the metatarsus, the four remaining parts constituting the tarsus. The femora and tibiæ are often bristly, and there may be spines on all the parts, which are always covered with either closely appressed or outstanding scales. The last segment ends in two claws or ungues, which in the female are always equal; in the male the fore and the mid pair are always

unequal in size, whilst the posterior ones are the same in size. The unguis in the female may be simple or uni-serrated (Fig. 85, ♀), in the male the fore and mid may be uni-, bi-, or even tri-serrated (Fig. 85, ♂). The legs are not subject to any marked modifications.

The halteres (*K*) need scant reference, as they do not possess any characters of diagnostic value. Roughly, they consist of a basal swelling, a narrow stem, and a swollen cup-shaped or funnel-shaped knob, which is usually scaly.

The abdomen presents but few features worthy of notice. It consists of eight segments, in the female terminating in two lobes, and in the male in distinct genitalia, consisting of basal lobes, claspers, and various prominences. The male genitalia are useful characters for separating very closely allied species. Except in the true *Anopheles* the abdomen is more or less coated with scales, and may have lateral tufts of scales and

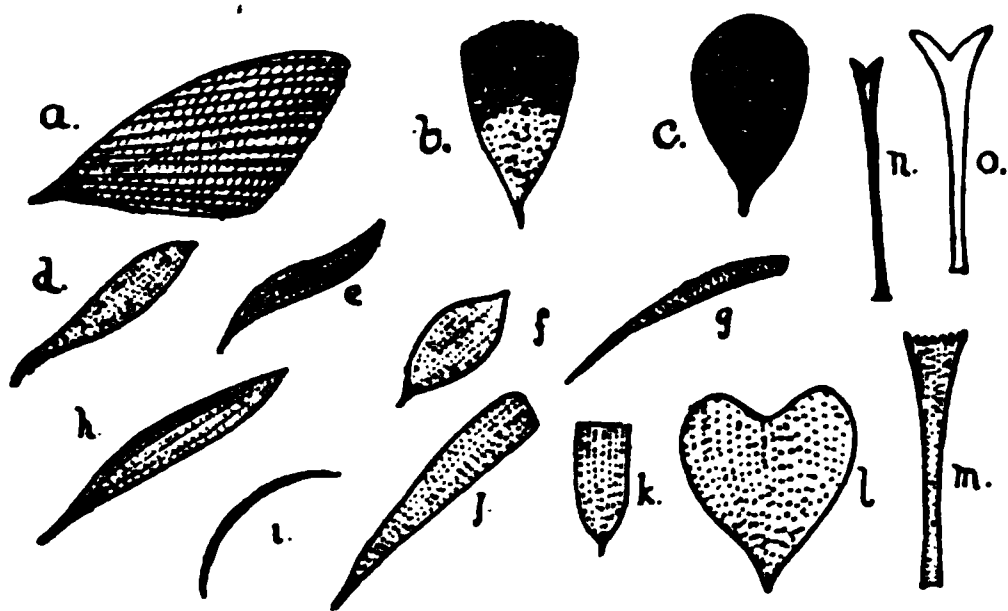


FIG. 87.—*a*, broad asymmetrical scale; *b*, parti-coloured scale; *c*, Cyclolepidopteron scale; *d* and *e*, broad and narrow-curved scales; *f*, spindle-shaped scale; *g*, linear scale; *h*, lanceolate scale; *i*, hair-like scale; *j*, Taniorhynchus scale; *k*, spatulate scale; *l*, heart-shaped scale; *m*, *n*, and *o*, upright-forked scales.

bristles. Each segment has a row or rows of bristles along its posterior border, and frequently many at the apex. In some Megarhininae there may be lateral fans of scales. Usually the body is straight (*Anopheles*, *Stegomyia*, etc.), but it may be curved (*Psorophora*), and notched below (*Gualteria*).

**Scales** (Fig. 87).—The most important characters by which mosquitoes can be grouped and identified are the scales. A few observers have attempted to ignore these important characters, but all the chief authorities on Culicidæ, such as Lutz, Goeldi, Leicester, Grabham, Ludlow, Blanchard, Ventrillon, Felt, have adopted them. The scales of the head are usually in three forms—(i.) narrow-curved scales (Fig. 87, *d* and *e*), (ii.) upright-forked scales (*m*, *n*, *o*), (iii.) flat or spatulate scales (*k*); in a few cases they may be (iv.) spindle-shaped (*f*), or (v.) twisted scales. The scales of the thorax are in the form of (i.) narrow-curved scales, (ii.) hair-like curved scales (*i*), (iii.) spindle-shaped scales, (iv.) flat spatulate scales, (v.) twisted scales. There are never upright-forked scales on any part of the thorax or abdomen.

On the abdomen the scales are usually (i.) flat spatulate forms, but they may be (ii.) spindle-shaped (*Cellia*), (iii.) narrow-curved (*Pyretophorus*), (iv.) twisted upright scales (*Mucidus*).

The scales of the wings are still more varied, and are—(i.) narrow, straight, linear scales (*Culex*) (*g*); (ii.) short, broad, spatulate scales (*Melanoconion*); (iii.) broad, straight scales (*Tæniorhynchus*) (*j*); (iv.) very broad, flat, asymmetrical forms (*Mansonia*) (*a*); (v.) heart-shaped scales (*Etorleptomyia*) (*l*); (vi.) long and short lanceolate scales (*Anopheles* and *Pyretophorus*) (*h*), and many others.

The scales of the wing-fringe are in three series (Fig. 85, *W*), long and short fringe scales, which are pointed, and small border scales, which vary in form, some spatulate, others of *Mansonia* type. Each vein has median vein scales and lateral scales, which usually differ in form (Fig. 85, *V*).

**The Internal Anatomy (Fig. 88).**—The mosquito's alimentary canal

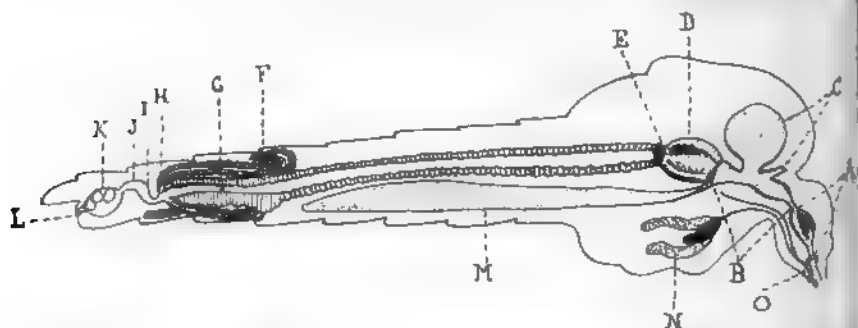


FIG. 88.—Internal Anatomy of a Mosquito. *A*, pharynx; *B*, oesophagus; *C*, dorsal reservoir; *D*, oesophageal valve and caeca; *E*, mid-gut begins; *F*, Malpighian tube; *G*, stomach; *H*, mid-gut ends; *I*, ileum; *J*, colon; *K*, rectum; *L*, anus; *M*, ventral reservoir; *N*, salivary glands; *O*, salivary duct. After Nuttall and Shipley.

and its accessory organs (*stomach*, *salivary glands*) are of paramount interest, because they contain the malarial parasites. The more complicated muscular system is also of importance, from the presence of the embryo *Filariae* in the thoracic muscles.

The more important parts of the internal anatomy can be easily dissected out, but the minuter elements, muscles and so forth, as well as the *Filariae* embedded in the thoracic muscles, must be shewn by serial sections. The alimentary canal really starts at the apex of the proboscis, the structure of which has been dealt with previously, and ends at the terminal anus. A pumping organ sucks the blood up through the tube formed of the labrum and hypopharynx. The hypopharynx itself is perforated by a small tube connected with the salivary glands, through which the saliva is ejected when the mosquito bites.

The various mouth-parts coalesce behind the clypeus; this spot indicates the actual *mouth*.

The mouth is followed by the buccal cavity, which opens into the



pharynx (Fig. 88, *A*) by a valvular arrangement. The *pharynx*, or pumping organ, by which the mosquito sucks up fluid, extends from the buccal cavity through the head or near to the back of the head, where it joins the œsophagus. It is tubular at its commencement, but subsequently becomes enlarged, and is much bigger in the female than in the male, and is partially chitinous. The *œsophagus* (*B*) is a very short tube which extends from the pharynx to the so-called œsophageal valve. Running from the œsophagus are three large blind sacs—food reservoirs—one ventral and two latero-dorsal (*C*); the large ventral reservoir (*M*) extends back to the seventh segment when filled with blood or vegetable fluids. The rather wild hypothesis was put forward by Colonel Giles, I.M.S., that these structures are analogous to the air-sacs of birds. That they act as food reservoirs was shewn by Dr. Nuttall and Mr. Shipley (17). Nor have they any connexion, as Grassi supposed, with the suctorial organs.

The œsophagus terminates in the so-called œsophageal valve (*D*), which is evidently homologous with the proventriculus of other insects. This serves as a valve between the œsophagus and the mid-gut, and has a number of protuberances, six according to Dr. Nuttall and Mr. Shipley, nine according to Grassi. I have seen four, so that they may vary in number in different species or genera.

The largest part of the alimentary canal is the mid-gut (*E* to *H*) or chylific ventricle, which consists of a straight tube running from the œsophageal valve to the stomach near the end of the body (*i.e.* about the level of the sixth segment). The “stomach” (*G*) is the posterior dilated portion of the mid-gut. It is here that the malarial parasites develop.

The *hind-gut* begins where the Malpighian tubes arise. It is short and slightly flexed, and is divided by Dr. Nuttall and Mr. Shipley into three areas—(*I*) ileum, (*J*) colon, and (*K*) rectum—and ends in the anus. The ileum is very short, and is often dilated near the mid-gut. The colon succeeds the ileum without any line of demarcation, whilst the rectum forms an oval cavity into which the colon suddenly opens.

The rectal space is much diminished by the protrusion of six rectal cæca. Each rectal cæcum consists of large cells, modified from the ordinary lining cells of the rectum, and a bundle of tracheæ pass up through the centre of each cæcum, which is covered externally with chitin. Their function is not definitely known, but is probably respiratory.

The *salivary glands* (*N*) are of much interest, because it is by their means that man is infected with the Hæmamœbidæ, Filaria, and the yellow-fever parasite. The salivary duct is not connected in any way with the alimentary canal, as Colonel Giles states. The saliva is ejected by the hypopharynx *via* the canal arched over by fine lamellæ. At the base of the hypopharynx is a structure connecting the common salivary duct and the groove. This is not a mere receptacle, but a *pump*, dependent on the action of powerful voluntary muscles. The common salivary duct (*O*) ends in the centre of a chitinous membrane which is continuous with a highly chitinous cup opening into the hypopharynx. The common duct passes back beneath the valve of the buccal cavity, where it divides into two



ducts of similar structure. These two salivary ducts run side by side along the ventral wall of the neck into the thoracic cavity; on reaching this region they diverge and branch out into the two salivary glands. Thus there is *no* connexion, as has been erroneously stated, with the alimentary canal. Each gland consists of three small blind cæca, which vary in position in different areas, because the glands have to accommodate themselves to the position of the very powerful thoracic muscles which propel the wings. These trilobed salivary glands are surrounded by fat-bodies, and are very large in proportion to the size of the mosquito. The three lobes of each salivary gland consist of acini of similar structure. For further details the reader is referred to Dr. Nuttall and Mr. Shipley's paper (17). In *Psorophora* each gland has five lobes.

The *Malpighian tubes* (*F*) are developed in the larva, and open at the same level into the hind-gut at the junction with the mid-gut. In the mosquito they are five in number, lie freely bathed in the fluids of the hæmocœl, and are richly supplied with tracheæ. They are pale yellow in colour when viewed with transmitted or reflected light, the colour being due to excretory products. That they are undoubtedly excretory organs is clear since uric acid and other renal products have been found in them in addition to concretions. In most Diptera the Malpighian tubules are four in number, but in all Culicidæ so far examined (*Culex*, *Anopheles*, and *Aedes*) they are five.

*Genital Organs.*—The female genital organs consist of a pair of ovaries opening into a common duct by the ovarian tubules. Into the common tube opens a mucous gland and also by a very long thin duct the spermathecae or chitinous sacs which store up, as usual, the spermatozoa.

The male genital organs consist of two testes united by vasa deferentia to the ejaculatory duct. To each vas deferens is attached a short sac, the

receptaculum seminis or vesicula seminalis. The penis is soft and fleshy, and is placed between two internal claspers, etc., and on each side of these are large external claspers which are structurally of much diagnostic value. The spermatozoa are round in form, with a flagellum.

The ova (Fig. 89) of mosquitoes are, like the adults, very varied in form in the different genera. Some are laid in masses called egg-rafts (*c*), the eggs being placed side

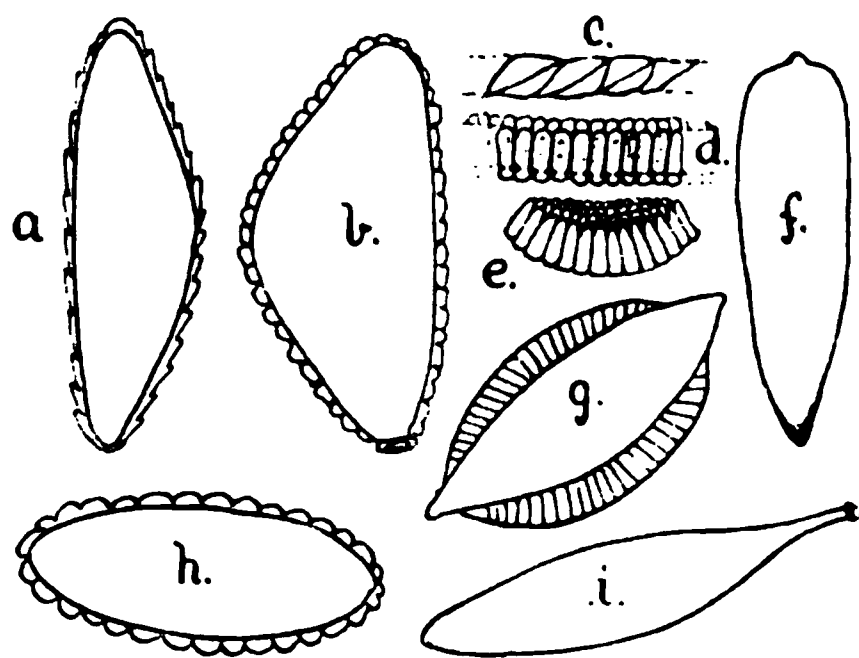


FIG. 89. —Culicine ova. *a*, ova of *Janthinosoma*; *b* and *c*, of *Chrysocnops fulvus*; *d*, of *T. fuscicollatus*; *e* and *f*, of *Culex*; *g*, of *Anopheles*; *h*, of *Stegomyia*; *i*, of *Mansonia*.

by side in their long axis (*Culex*, *Scutomyia*), others are laid in long ribbons (*Tæniorhynchus*) (*c* and *d*), yet others separately (*Stegomyia*, *Mansonia*, *Janthinosoma*) (*h*, *i*, *a*). Their form differs widely in the

various genera. In *Culex* they are bottle-shaped, in *Mansonia* the neck is long, in *Stegomyia* they are oval, and in *Anophelinae* oval with distinct lateral floats. Those in each group may be told by minor structural differences. In the malarial *Anophelinae* the sculpture and form of the floats are most useful for purposes of differentiation. In most cases the ova are laid by the female on water (*Culex*, *Anopheles*, *Janthinosoma*), but they may be laid on damp mud (*Grabhamia*), or on leaves (*Dendromyia smithi*). The length of time the eggs take to incubate varies in different species and at different times. In *Culex pipiens* they will give rise to larvæ in from four to six days after deposition, in *C. fatigans* in two or three days; in *Megarchinus* they take much longer, and also in *Grabhamia* if, as often happens, they are placed on mud. In *Stegomyia* the eggs can withstand prolonged desiccation. Some I received by the courtesy of Dr. Finlay from Cuba remained two months after arrival in a test-tube and then hatched (20, vol. iii. p. 6).

The larvæ fall into two markedly separate groups which we may designate as Siphonate and Asiphonate. The latter are always those of the *Anophelinae*. All Culicid larvæ are aquatic throughout the whole of their existence. They not only occur in fresh water but in sea-water, Dr. Bancroft having found several (*Mucidus alternans* Westwood, *Culex marinus* Theobald) which breed freely in salt water, and some have been found in damp mud. Practically all kinds of collections of water are acceptable to the larvæ: some prefer rain-water barrels, cisterns, and the water in tins, calabashes, and jam-pots; others ponds, slow-running streams, and along the banks of large rivers, others live in the water collected in bromelias (Lutz), and in the water that collects in hollow bamboos, gaining their entrance through exit holes left by boring insects (*Leicester*). Others live in pitcher-plants (*Nepenthes*, etc.). The domestic forms which are best known usually choose barrels and cisterns. The importance of the sylvan species is, however, just as great, as it is by means of these that fever is contracted in the jungle as well as in the habitations of man.

The typical form of siphonate larvæ is best seen in *Culex* (Fig. 90).

The head is provided with dorsal and other chitinous plates, and is either rounded or irregular in form; there are usually a pair of compound eyes and ocelli. The appendages are in the form of two short antennæ, mandibles, maxillæ, a distinct clypeus, and numerous sensitive hairs. The thorax is

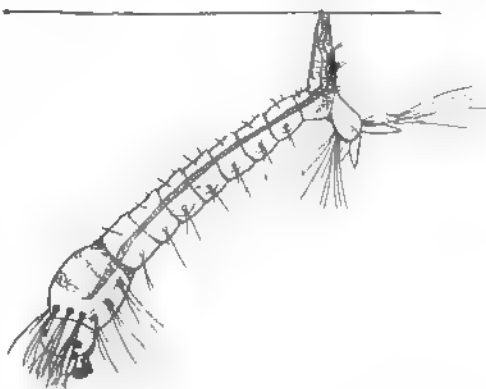


FIG. 90.—Larva of a Culicine showing siphon

usually large, and carries on each side bunches of bristles of varied form, and others dorsally. The abdomen is composed of nine segments, the eighth bearing on its dorsal surface the respiratory siphon or air-tube. The siphon varies in length and form in different genera: in *Culex* it is long, in *Grabhamia* and *Stegomyia* short and thick, in *Melanoconion* very long and thin, in *Tæniorhynchus* it is thick at the base, much contracted apically, etc. It also varies in form at different stages of growth. The siphon has on it a series of spines called the "comb"; the form and number of these "comb" spines distinguish the different species of larvæ together with the number and form of the spines seen in the basal comb on the eighth segment. The ninth segment is short, and bears the anus as well as four variously formed plates, which contain air-tubes, and also numerous bristles with a definite arrangement. The anterior segments bear simple and branched lateral and dorsal hairs.

Asiphonate (Fig. 91) larvæ all belong to the section *Anophelinae*, the only group so far that has been shown to have any relation with malarial fevers. The typical Anophelete larva may be taken in *Anopheles maculi-*

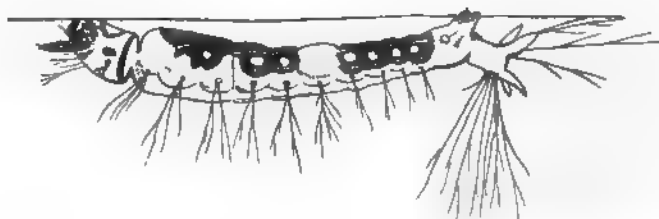


FIG. 91.—Larva of *Anopheles*. After Howard. (Asiphonate form.)

*pennis* Meigen, not only because it is the type of the genus *Anopheles*, but because it is the only one so far satisfactorily figured. The asiphonate larva, like the preceding siphonate form, has the body divided into head, thorax, and abdomen, the head is relatively smaller than in the siphonate forms, the thorax shews no signs of segmentation, and the abdomen consists of nine segments—the eighth is devoid of the respiratory siphon seen in *Culex*, *Stegomyia*, etc. On the fore border of the head of the asiphonate Anopheline larva are four chætæ which present certain peculiarities. These so-called "frontal hairs" (Fig. 92, *F*) have been erroneously regarded as of specific importance, but, as shewn by Dr. Nuttall and Mr. Shipley's accurate illustrations (16), the frontal hairs are different in various stages of the larva of *Anopheles maculipennis*. Unless the exact age of a larva is known, it is unsafe to attempt to determine the species by these structures, for they vary in different stages, any work based on such observations must therefore only be accepted tentatively until years of experiment shew larvæ figured at each moult. The structure of the antennæ apparently varies in like manner according to age.

The adult larvæ have many branched or plumose hairs on the thorax;

these are usually fewer and simpler in the young form, or a few only are plumose. The thorax is usually very much broader than the head or abdomen, and more so in the adult than in the younger stages. The abdomen is composed of nine segments, more or less deeply constricted. As a rule the first three in the adult larvæ bear plumose setæ, whilst in the young they are simple; the remaining segments have long simple setæ, whilst all have small branched ones in the adult and not in the young forms. Peculiar structures are found on the dorsum of some of the segments in the form of the so-called "palmate hairs" (Fig. 92, I'). These are paired, and are composed of a short stem and foliate rays spreading out in a star-like manner. They differ in number and form in different species, and these again are not noticeable in the young larvæ. On the eighth segment are placed the two respiratory openings, which are but slightly raised above the body surface, no trace of a siphon as seen in *Culex* being present. The last segment has four small anal gill-plates, dorsal plumose and branched hairs, and a prominent ventral pair of long branched setæ.

The characters of specific value are the frontal hairs and palmate hairs,

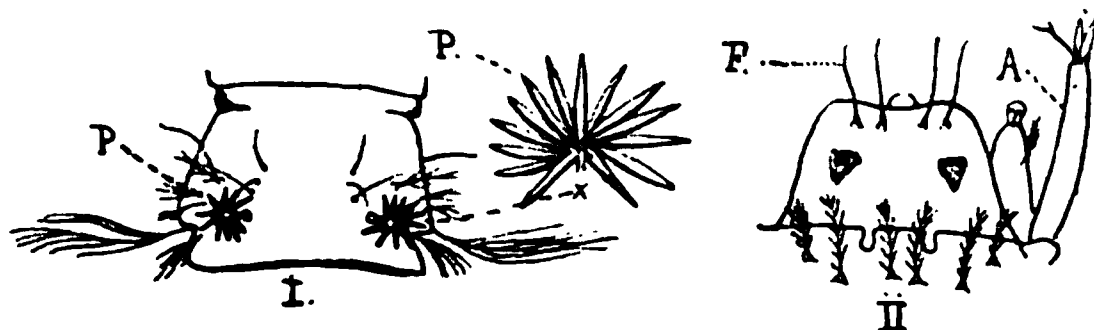


FIG. 92.—I. Larval segment; P. palmate hairs. II. Head shewing F, frontal hairs, and A, antenna. Partly after Nuttall and Shipley.

but the student is warned to take these characters with great caution, because of their variability in different stages and the similarity of different species in the different periods of growth.

Larval Anophelines mainly prefer natural collections of water, but they may be found in rain-barrels, etc. (*A. maculipennis*). Their colour is usually grey, pale brown, dull green, or mottled grey and brown. The head has frequent characteristic marks on the occiput. The position of Anopheline larvæ in the water is usually nearly parallel to the surface when they are respiring, the air-holes on the eighth segment and the palmate hairs being at the level of the surface film. This is contrary to what we find in most Culicines, which hang more or less head downwards, whilst the long or thick siphon is touching the surface film. In a few Culicines—*Grabhamia jamaicensis* Theobald, for instance—the larva lies nearly parallel with the surface, as in the Anophelines, in spite of its rather long siphon.

Most Anopheline larvæ live but a short time; a few, however, live many months, such as those of *Anopheles bifurcatus* Linn., which pass all the winter in Europe in the larval stage. The larvæ of Culicidæ are frequently known as "wrigglers."

The next stage is, as in all other insects, called the pupal stage. The pupæ, although they take no more nourishment than the pupæ of

butterflies or moths, are nevertheless active, wriggling about in a series of curious jerky movements in the water, and constantly coming to the surface to breathe. Although the pupæ do not present such marked generic and specific characters as the larvæ, there are very varied types to be found. The main points of difference may be detected

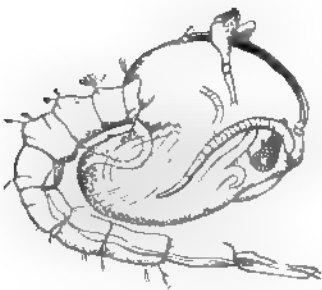


FIG. 93. Pupa of *Anopheles*. After Nuttall and Shipley.

in the air-tubes and the anal fins. The typical pupa (Fig. 93) has a large head and thorax, and a long thin curved abdomen ending in two anal plates. The head is folded down upon the thorax, and bears two very large and conspicuous black eyes. The thorax bears the outline of legs and wings, and on its dorsal surface a pair of trumpet-shaped bodies, the respiratory siphons. Thus in the pupa the respiratory organs open on the thorax instead of on the abdominal surface as seen in the larva, and are double instead of single.

The nine-segmented abdomen ends in two broad anal plates, which vary in form in the different groups, but all have a central rib. The thoracic siphons vary in the different groups: in true *Culex* they are narrow and cylindrical, in most *Anopheles* they are broadly funnel-shaped, in the *Mansonia* they are irregularly curved, in *Limatus* they are very small and thin. When the pupa wishes to breathe it comes to the surface like the larva, and the two siphons come in contact with the surface film and take in air.

The duration of pupal life in a mosquito is usually very short, in some cases less than forty-eight hours, but it may be as long as ten or twelve days. The effect of heat on the rate of pupal development is very marked, much more so than on the larvæ.

Pupæ are usually brown or green in colour; some few show dull reddish hues.

**Hatching of the Pupæ.**—When the pupæ are ready to hatch, they rise to the surface of the water and straighten themselves out. The shell or skin then splits over the thorax, and the adult gradually withdraws its body from the pupal case. They rest for some little time on the skin, which forms, as it were, a raft, until their integument and wings have hardened. The time of emergence varies in the different mosquitoes: some mainly emerge in the early mornings, others at midday. Very large numbers of imagines get destroyed during emergence; the least wind will upset the frail craft they are settled on, and they fall into the water before their wings are sufficiently dry to enable them to fly.

**Natural Enemies of Mosquito Larvæ and Pupæ.**—The natural enemies of mosquitoes living in small artificial collections of water are very few, but in larger and natural masses of water they have many enemies. Chief amongst these are fish and certain aquatic insects. In addition, the

mosquito larvæ and pupæ are preyed upon by a parasitic worm, a species of *Mermis*, which according to Leuckart may have been a not unimportant factor in destroying mosquitoes near Leipzig. A certain number of Sporozoa seem also to be parasitic on the young stages, but none of them do any real good in lessening their numbers. A species of tick (*Ixode*), so far undescribed, exists in its immature stage on mosquito larvæ, and develops into the adult on the mature fly. This tick is a small red cherry-like body frequently to be seen on certain mosquitoes, especially Anophelines. These larvæ were first shewn me some years ago by Dr. Cropper, and the adult ticks were first pointed out to me by Dr. Balfour in Anophelines from the Sudan. By far the most important enemies are certain kinds of fish. Minnows, especially of the genus *Fundulus* and *Gambusia*, feed ravenously on them, and sticklebacks (*Gasterosteus*, etc.), carp, and numerous other kinds, help to keep these pests down; on the other hand, some fish and mosquito larvæ live comfortably side by side in the rice-fields of India. Certain species of fish, however, are undoubtedly of great benefit. The predaceous larvæ of the dragon flies (*Odonata*) and water beetles (*Hydrophilidæ*) devour the larvæ and pupæ very rapidly. The adult mosquitoes are preyed upon by dragon-flies, insectivorous and many night-flying birds, such as night-hawks, and by bats in all parts of the world, but mosquitoes multiply so rapidly, and their numbers are so immense, that their prevalence is only slightly restricted by natural enemies. In certain seasons great numbers of the adults are killed by a fungus similar to that which attacks the house-fly. This fungus, known as *Empusa culicis* Braun, is common to the United States and Europe. The mosquito is found attached to leaves, stones, sides of barrels, etc., by threads which proceed from the mycelium infecting its body. In a district in Britain, known to me, both *Anopheles maculipennis* and *Culex pipiens* were practically exterminated by this fungus.

**Habits of Adult Mosquitoes.**—Most mosquitoes are nocturnal feeders, but it is too often forgotten that some are not, and that mere protection of the mosquito-net at night is not an infallible preventive of malaria or of yellow fever. Many *Anopheles* commence to bite some time before sunset, and I have even known *Anopheles bifurcatus* bite in the middle of a summer's day. The yellow-fever carrier (*Stegomyia fasciata*) bites most viciously between the hours of 1 and 3 P.M., but may do so also at night or at any other time. That Anophelines have this habit in the tropics is clear from Sir William Macgregor's statement: "I first saw *Anopheles* on the afternoon of the first day we visited the West Coast of British New Guinea. We had all sufficient experience of it before night, for it is not the case that *Anopheles* bites only at night, nor that its puncture is always painless."

The majority of dingy-coloured species (Anophelines, *Culex*, *Melanoconion*, etc.), however, undoubtedly prefer night for feeding. During the day they hide away amongst shrubs and bushes, in dark corners of native huts, tents, and houses. Certain species shew a decided

preference for settling on dark objects, and dark clothing undoubtedly attracts them. This is especially noticeable as regards *Stegomyia fasciata*. Many of the brilliant kinds, such as the Megarhininæ and Sabetinæ, are day-fliers, and delight in the brightest sunshine. Certain species shew a decided preference for houses and huts, others are purely sylvan. The domestic or household Culicidæ, such as *Culex pipiens* Linn., *Culex fatigans* Wied., *Stegomyia fasciata* Fabr., seldom occur far from habitations. That they may do so, however, was shewn by Dr. Bancroft, who found the latter a long way from any dwellings in the Queensland scrub. Conversely, the sylvan species may invade houses in the tropics. According to Dr. Daniels, habitations built in small clearings are not much infested with sylvan mosquitoes. On the other hand, in larger clearings, in which small towns, villages, mining quarters, etc., are built, with little or no jungle close to the houses, sylvan mosquitoes are found in abundance, and breed in bath-tubs, water-barrels within and outside the buildings. The best example of this is *Stegomyia scutellaris* Walker, which may become domesticated in large numbers. Certain species are limited to the littoral (*C. cancer* Theobald), where they breed in crab-holes, and are never found far inland.

The distance these insects fly is not definitely known, but it is assumed that they do not journey very far. A mile probably would be an approximate limit. As a rule during boisterous weather they seek shelter, so that it is not very likely that wind acts to any extent as a distributing agent.

When at rest different species assume different positions. In most cases an Anopheline at rest can be recognised by its general resemblance to a thorn stuck in the ceiling or wall, the proboscis and body being much in one line, whilst in Culicines there is an angle formed between proboscis, head, thorax, and the abdomen giving a hunchbacked appearance; in both the hind legs are free from the resting surface. This rule is not absolute, however, for according to Col. Giles one Anopheline (*Myzomyia culicifacies*) rests in a similar position to *Culex*. But it serves as a rough means of deciding between a possible malarial and non-malarial species.

The distribution of mosquitoes may be said to be world-wide. They occur in vast numbers in the arctic regions as well as in the tropics. If anything, they swarm in greater numbers in tropical countries, especially in Africa, than in subtropical and arctic regions. The temperate zone seems most free from their ravages. South America is particularly rich in species belonging to the Aedinae, and poor in Anophelinae. India and Asia generally, and Africa, on the other hand, have a large number of Anophelinae. *Culex* is a world-wide genus, occurring from the arctic regions to the equator. The Mansonias occur only in warm climates, notably Central Africa, Asia, and South America; Grabhamias in most abundance in Europe and North America; the genus *Stegomyia* (sen. st.) between 40° N. and S. of the equator. A few genera are confined to certain countries: for instance, *Psorophora* does not occur



outside the Americas; *Sabethes* is limited to the South American continent; *Hæmagogus* to South America and the West Indies. Very few genera occur in temperate climates; the typical temperate genera are *Anopheles*, *Theobaldia*, *Culex*, *Grabhamia*, and *Aedes*. Both the former occur elsewhere, especially in the hill districts of warm climates, such as *Anopheles gigas* Giles, *A. lindsayi* Giles, *Theobaldia glaphyoptera* Schiner, in the hill districts of India. Altitude is no safeguard against mosquitoes, for they swarm at 13,000 feet in the Himalayas, and are just as annoying as at the sea-level in Scandinavia.

There is no doubt that they occur in greatest abundance in damp, marshy places and along river-courses and the borders of large lakes, but they also breed in numbers in almost bare rocky spots, using the small collections of rain-water such as collect in the hollows of granite boulders.

*The distribution of certain species* is very wide. These all prove to be domestic mosquitoes. The two with the widest distribution are the yellow-fever carrier (*Stegomyia fasciata*) and the common brown household mosquito (*Culex fatigans*). The yellow-fever carrier occurs in greatest abundance in Central America, in Northern South America, and the West Indies, but it is found in great numbers in North America, it is found in India, is very abundant in Australia, in Africa it occurs in many parts both in the north and south, and seems to be making its way steadily up the Nile. In Malaya it occurs in many of the ports, and this is true for many other countries where it is not present inland. It is present in most oceanic islands as one of the typical mosquitoes. It comes well into Southern Europe, but I do not think it will ever become domesticated in Britain or any part of Northern Europe. We may expect it to occur anywhere between 40° N. and S. of the equator.

*Culex fatigans* Wiedemann has a very similar distribution, and seems in many places to live side by side with the *Stegomyia*, but I have not yet seen specimens from Europe; probably it occurs in the southern regions, but has been confused with the *Culex pipiens* Linnaeus, a closely related species. The gradual spread of this brown mosquito has been noticed in Australia farther and farther inland by Skuse, who supposed it to be a variety of *Culex ciliaris*, a synonym of *Culex pipiens*.

Many other species have a wide distribution; for instance, the quaint little *Aedeomyia squamipenna* of Arribáizaga, which occurs in South America and the West Indies, in the Malay Peninsula, in India, the East Indies, and has recently made itself known in the Sudan.

The spotted-winged Culicine *Theobaldia annulata* Meigen occurs in Europe and North America; the related *Theobaldia spathipalpis* Rondani in Southern Europe, the Mediterranean Islands, Madeira, Algeria, Cairo, Khartoum, and the Cape. The *Theobaldia glaphyoptera* Schiner has recently been sent me from the Himalayas, otherwise it is only known in Europe. Many of our European species occur in North America (*Culex fatigans* Meigen, *Culex nigripes* Zetterstedt (called *C. impiger* Walker in America, etc.). In fact, so erratic is the distribution of these insects that



we may expect them to appear in almost any part of the globe, and far from the original home of the described specimens. There are two ways in which these strange points in distribution can be explained : first, that so far but little is known of the Culicidæ, and that the species in question may exist in the intervening areas. It is doubtful if this will explain most of the cases. The countries where many such instances occur have been very thoroughly investigated, and it seems most improbable that such well-known insects as *Culex cantans* and *Theobaldia spathipalpis* have been overlooked where many collectors have been at work. The glacial period may explain a few such cases ; for example, the presence of northern forms in isolated hill regions, as *Culex cantans* in the Ghats and *Culex nigripes* in the Himalayas. But there is no doubt that artificial distribution will explain most of these phenomena.

*The Artificial Distribution of Mosquitoes.*—Mosquitoes that are more or less domesticated, such as those just referred to, are undoubtedly distributed over the globe by artificial means. Mosquitoes are carried across the sea by ships in two ways : by the adults being carried in a dormant condition, and by means of the larvæ living in ships' tanks. The danger of this means of transit is very great under favourable conditions. Infected mosquitoes may leave a yellow-fever port and may fly off to another port when the ship is unloading and carry the fever with it, as well as form a nucleus of a colony of mosquitoes previously unknown in the port. We may note here that in Malay *Stegomyia fasciata* at present only occurs in the ports. Water transit will carry them still farther inland. It is well known that they are carried up rivers, and thus farther and farther inland, by steamers. Transit by means of boats is thus very important, and also explains the wide distribution of *Culex fatigans* and of *Theobaldia spathipalpis* in recent times. There is no doubt that the latter, which occurs in privies and houses, has made its way to the Canaries and then to the Cape, and similarly by steamer to Egypt. It was certainly in this way that *Culex fatigans* reached Australia. Having crossed large tracts of ocean by means of steamers, they are not content to stay at their port of landing. *Culex fatigans* has spread inland in Australia, following the advance of the railways. It is quite as common to find these flies on the train as on board ship. Artificial, not natural, means of distribution explain the erratic distribution of these insects ; for it is only the domestic species that are so widely spread over the globe. Certain factors regulate this distribution. *Stegomyia fasciata* might come to Britain. It would not live here, but if it landed at Lisbon or Naples it would. The distribution of each species is limited ; tropical and sub-tropical species will not live in Northern Europe, but Southern European species will live in warm places. These means of transit cannot be neglected in the light of our knowledge that infection may be carried by the insects under certain conditions and within certain climatic limits.

Nature also spreads these insects. Larvæ get carried down by the stream of rivers, and wind blows the adults now and again some distance,

and eggs get washed still farther by running waters, but these factors are only active within comparatively small areas.

**The Food of Mosquitoes.**—There is no doubt that the majority of mosquitoes never taste human blood, and it is certain that but few take vertebrate blood. Certain species, however, are blood-suckers. The *Grabhamias* and *Stegomyias* are particularly so, and also *Mansonias*. Many *Anophelines* are also very blood-thirsty, and the same may be said of the *Uranotænia*s, *Dendromyias*, and certain species of *Culex* and *Culicada*. The majority feed upon vegetal juices; I have frequently seen *Culicids*, both males and females, on *Compositæ* sucking the juices. Recently the spotted-winged *Anopheles* (*A. maculipennis* Meigen) have been found feeding and gorging themselves on the nectar from ivy blossom. Professor Ronald Ross, Dr. Bancroft, and others have frequently pointed out that they feed on bananas, and that they may be kept alive by feeding them on banana slices. Professor Ross, speaking of them in West Africa, says: "They (the mosquitoes) began to fly about and walk over the fruit, plunging their probosces into it in many places, so that the banana was sometimes covered with gnats both male and female." Decaying apples have also been observed to form food for *Culex pipiens* (20, vol. i. p. 69).

Many *Culicidæ* also take the blood of invertebrate animals, such as insects. They are also stated to feed upon young fish, attacking their heads and even killing them. The strange part is that certain species suck human blood in some places and yet do not in others. *Anopheles maculipennis*, a proved malaria-carrier, bites viciously in many parts of Europe, but in some districts in Britain it is never known to bite man. The same applies to *Culex pipiens*. The females alone have this blood-loving habit, the males being plant-feeders only. One doubtful record is given by Ficalbi, who states that the male *Stegomyia fasciata* may occasionally bite man, but the study of its mouth-parts disproves this. The statement frequently made that the female mosquito must have a meal of human blood before she can deposit fertile eggs certainly does not apply to all species. Professor Ross and others have made observations confirming this statement, so that it is probable that some species do require human blood. On the other hand, Sir William Macgregor tells us that he camped "for weeks at a time in the mud and swamps of the western or *Anopheles* country of British New Guinea and yet left without any cases of fever, the reason being that for some one hundred and fifty miles of coast there were no human inhabitants, which seems clearly to prove that human blood diet is not necessary for the breeding of *Anopheles*." I have bred *Anopheles maculipennis* and *Anopheles bifurcatus*, neither of which had any human or vertebrate blood, but yet deposited fertile eggs, and have frequently found this to be the case with *Culex pipiens*. Further, according to Professor Howard, countless swarms of mosquitoes breed in the vast stretches of swampy land in America into which warm-blooded animals never find their way. It may therefore safely be said that mosquitoes breed mainly without the stimulus of human blood.

**How Mosquitoes pass the Winter.**—In warm climates mosquitoes may continue to breed all the year in small numbers, but during the dry season they rest. In temperate and cold regions they may pass the winter months in three ways—as adults, as larvæ, and as ova.

The common spotted-winged European *Anopheles maculipennis*, the common gnat *Culex pipiens* hibernate in the adult stage. They take up their abode in cellars, attics, out-houses, poultry-sheds, and stables, usually seeking dark corners in which to hide. So far as we at present know, the females alone hibernate, the males dying off at the approach of cold weather. These hibernating females have been fertilised by the males prior to their taking up winter quarters. This winter hibernation is sometimes broken during a spell of warm weather, and hence we can account for winter malaria. The unspotted-winged *Anopheles bifurcatus* and *A. nigripes* pass the winter in the larval stage, and are not in the least affected by the hardest frosts; nor are the larvæ of *Dendromyia smithii*, which live in pitcher-plants and which can be frozen and thawed many times. The European *Grabhamias* may remain as ova during the winter in mud, at least I have observed this in the case of *Grabhamia dorsalis* in Britain. Dr. Christophers states that “in the dry season in Sierra Leone the *Anopheles* exist in most parts of the town (Freetown), in dwellings, especially in overcrowded native huts and native quarters, ready to lay eggs when pools appear.” Amongst the situations in which mosquitoes are found to shelter during colder or dry weather in tropical climates must be mentioned curtains and draperies generally.

**Effect of Weather on Mosquitoes.**—Mosquitoes are susceptible to changes in the weather. A certain amount of rainfall is essential to them: a moderate rainfall which forms great numbers of pools and fills up vessels, jars, cut bamboos, and the like, naturally gives them greater breeding facilities, whilst, on the other hand, a long spell of dry weather acts in the reverse way. Mr. Tait, medical officer of the Cayman Islands, noticed there that “a slight rainfall, followed by heat, appears to favour their increase, whilst a continuous shower or a high wind is destructive to them.” Undoubtedly a moderate rainfall, just sufficient to fill up the pools and holes in the rocks, is most favourable to their increase. Heavy torrential rains are harmful, for they wash out the small pools and vessels and thus destroy numbers of larvæ and pupæ.

Prolonged frost does not seem to affect the larvæ all alike. Some species are said to be killed when ice accumulates on the surface. But those species, like *Anopheles bifurcatus*, which winter as larvæ in Europe, are not in the least affected by frost. Ice two inches thick has been noticed over them for a week, and yet they all pupated and hatched out in the following spring. The same may be said concerning some of the hill species in India and the *Dendromyia* previously quoted. Winds are prejudicial to mosquitoes, especially if they are strong at the time of hatching; the frail crafts composed of the pupal skins are blown about and get upset, and so the mosquitoes are thrown into the water before they are capable of flying.

**Certain Water Plants inimical to the Larvæ.**—It is said that water thickly covered with green water-weeds, such as *Lemna*, does not contain mosquito larvæ. This is true in certain cases where the pools are so densely covered that the surface of the water is completely hidden. In a serious outbreak of mosquitoes (*Culex nemorosus*) in Epping Forest this was particularly noticeable. Colonel Giles has noticed in the Benares Public Gardens, where there are scores of small irrigation tanks, that both *Culex* and *Anopheles* larvæ were present in every tank except in those that were covered with a peculiar floating weed, looking much like young lettuce, called by the natives *Jalkumi*. Pools that are filled with the green slimy *Spirogyra* contain no larvæ, for they become entangled in the threads of weed and so cannot reach the surface to breathe. Professor Smith says that the presence of even a small quantity of weed seems to act almost as a poison to the larvæ.

Various plants have the reputation of keeping mosquitoes away from habitations, but so far none have been found to be of any use. Castor bean plants were thought to have this effect, but experience has shewn that mosquitoes will even settle to rest under the leaves.

**The number of mosquitoes** described is roughly eight hundred. Very few of these are known to be in any way connected with diseases, and by far the greater number are purely sylvan insects, and so are not so well known as those occurring in man's habitations. One hundred and three species of *Anophelinæ* are described at present. A few of these are doubtful, and some two dozen are founded on very uncertain characters, and will probably prove to be merely varieties of other species. Many of the types of old species have been lost, and as the descriptions are so brief, we cannot be certain as to actual identification. These must be given up as lost species.

**How to Mount and Examine Mosquitoes.**—The adult mosquitoes should be preserved in two ways: as dry specimens, and as dissections mounted in Canada balsam.

The best plan to mount them dry is to pin the mosquito on a disc (Fig. 94). This is done by using a very fine (No. 20) silver pin (*b*) pierced through a card disc (*a*) which can be either punched out of fine stiff cardboard or bought. The fine pin will bend on being forced through the card disc, so that we must first just pierce the disc with the point of a needle sufficient to break the surface. Care must be taken not to pierce the disc so much that the fine silver pin can move about. Having done this, the point of the No. 20 pin is forced through the thorax of the insect, so that its apex just protrudes through the dorsum. The legs and wings may then be spread out on the disc so as to expose them, and the disc fixed to a cork-lined air-tight box by a larger, stout pin (*e*), forced through one side of the card.

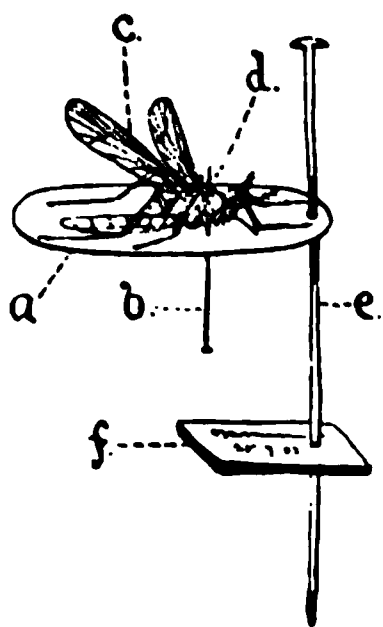


FIG. 94. *a*, card disc; *b*, No. 20 silver pin; *c*, insect; *d*, point of *b*; *e*, large pin; *f*, label.

The data concerning the specimen can be conveniently written on the under side of the disc, or may be attached as shewn in the figure as a label (*f*).

To examine the whole insect microscopically, a two-third of an inch power is necessary. This may be done by simply pinning the specimen on a cork plate, or by taking the large pin out of the disc and placing the small pin through a hole made in a piece of cardboard. By gradual movement of the specimen all parts of the dorsum, legs, and wings can be seen. The scales on the head should be first examined, then the thorax, as these two areas are of great diagnostic value. The scales on the scutellum are best seen by turning the insect in the reverse direction, that is, with the abdomen pointing towards the light. The abdomen can be examined at the same time. Most genera can be recognised by the squamose characters of the head, mesothorax, and scutellum, but in the Anophelinæ the scale structure or absence of scales on the abdomen must also be taken into account.

To examine wings and legs properly the parts must be dissected off and mounted, so that they can be examined perfectly flat. Unless this is done, the true form of the wing-scales and the relative proportion of the venation cannot be seen, nor can the structure of male and female unguis be made out with any degree of precision—all most important specific characters, whilst the wing-scales are of generic value. (Note the wing-scales of *Mansonia*, *Culex*, and *Tæniorhynchus*.) The wings are best mounted dry, as any media have a tendency to make the scales so transparent that they often cannot be seen. If any media be employed, balsam dissolved in Venice turpentine is the best. To examine the unguis the last few tarsal segments should be mounted in xylol-balsam, the cover-glass being well pressed down on the slide so as to separate the two claws on each foot. The structure of palpi can only be made out by microscopic preparations. The whole head may be soaked in eau-de-javelle and then mounted in xylol-balsam. The male genitalia should also be mounted in balsam and subjected to slight pressure, and prepared so that the one-sixth power may be used on them as well as the two-thirds. The apex of the abdomen may be cut off, with the genitalia attached, and mounted; this will be found to give better results than using the whole abdomen. Larvæ must be mounted in balsam. To obtain satisfactory results two preparations are necessary—one in a shallow cell, the other flattened out, so as to shew as a transparency, and so expose the clypeus and siphon combs. Larval *skins* are usually best adapted for this purpose. No wings should be described unless perfect flattened preparations have been made; numerous errors have crept in, as descriptions have been drawn up from crumpled wings.

## Classification of Mosquitoes

The earliest classification, based on the characters of the palpi, contained three genera, namely, *Anopheles*, *Culex*, and *Aedes*. In the first the male and female palpi are long, in the second the male palpi are long and the female short, and in the third they are very short in both sexes. To these three genera were later added the genera *Sabethes*, *Psorophora*, *Megarhinus*, marked tropical forms quite unlike the first three. It was not until 1891 that fresh genera were formed, when Arribáizaga created several new genera out of *Culex*, including *Janthinosoma*, *Tæniorhynchus*, *Ochlerotatus*, and *Heteronychia*, and in doing so attached great importance to the palpi. Scarcely any fresh species and only one fresh genus was described (*Hæmagogus* Williston) between 1891 and 1901, when the *Monograph of the Culicidæ of the World* (20) commenced to appear. In this work I pointed out that the examination of a very large amount of material, from all parts of the world, shewed that palpal characters would not hold as of diagnostic value above the rank of species. The characters most constantly found and most easily observed, and by which previously existing genera could be split up into smaller groups, were shewn to be the scales of the body, head, and wings, etc. It is essential to bear in mind that scales are particularly characteristic of the whole family Culicidæ. The primary grouping, however, was temporarily retained in vols. i., ii., and iii. of the *Monograph*, but genera were separated by squamose characters. It is interesting to note that Felt, working on the male genitalia, finds that as generic characters they endorse those taken from the squamose structure.

The incongruousness of the diagnostic value of palpi as being of generic value is seen best in the case of the closely allied genera *Megarhinus* and *Toxorhynchites*. In the former the palpi are long in both sexes, and thus would come in the *Anopheline* group, whilst in the latter the female palpi are short, and so would come in the *Culex* group, and yet both these genera are closely related in every other way. The classification previously adopted is briefly as follows:—

### Culicidæ

A. Proboscis formed for piercing ; wings with six long veins.

I. Palpi long in ♂.

A. Metanotum nude.

a. Palpi long in ♂ and ♀ ; in the ♀ not quite as long as the proboscis.

1. First submarginal cell as long or longer than the second posterior cell . . . . . Sub-fam. *Anophelinae*.

2. First submarginal cell much smaller than the second posterior cell. Proboscis curved

Sub-fam. *Megarhininae*.



β. Palpi long in ♂, short in ♀.

3. First submarginal cell much smaller than the second posterior cell; the proboscis curved

Sub-fam. *Toxorhynchina*.

4. First submarginal cell as long or longer than the second posterior cell. Proboscis straight

Sub-fam. *Culicina*.

B. Metanotum with squamæ or chætæ, or both.

5. Palpi long and acuminate in ♂, short in the ♀

Sub-fam. *Trichoprosopina*.

II. Palpi short in ♂.

Palpi short in both sexes, often very minute

Sub-fam. *Aedeomyia*.

B. Proboscis formed for piercing; wings with seven scaled long veins.

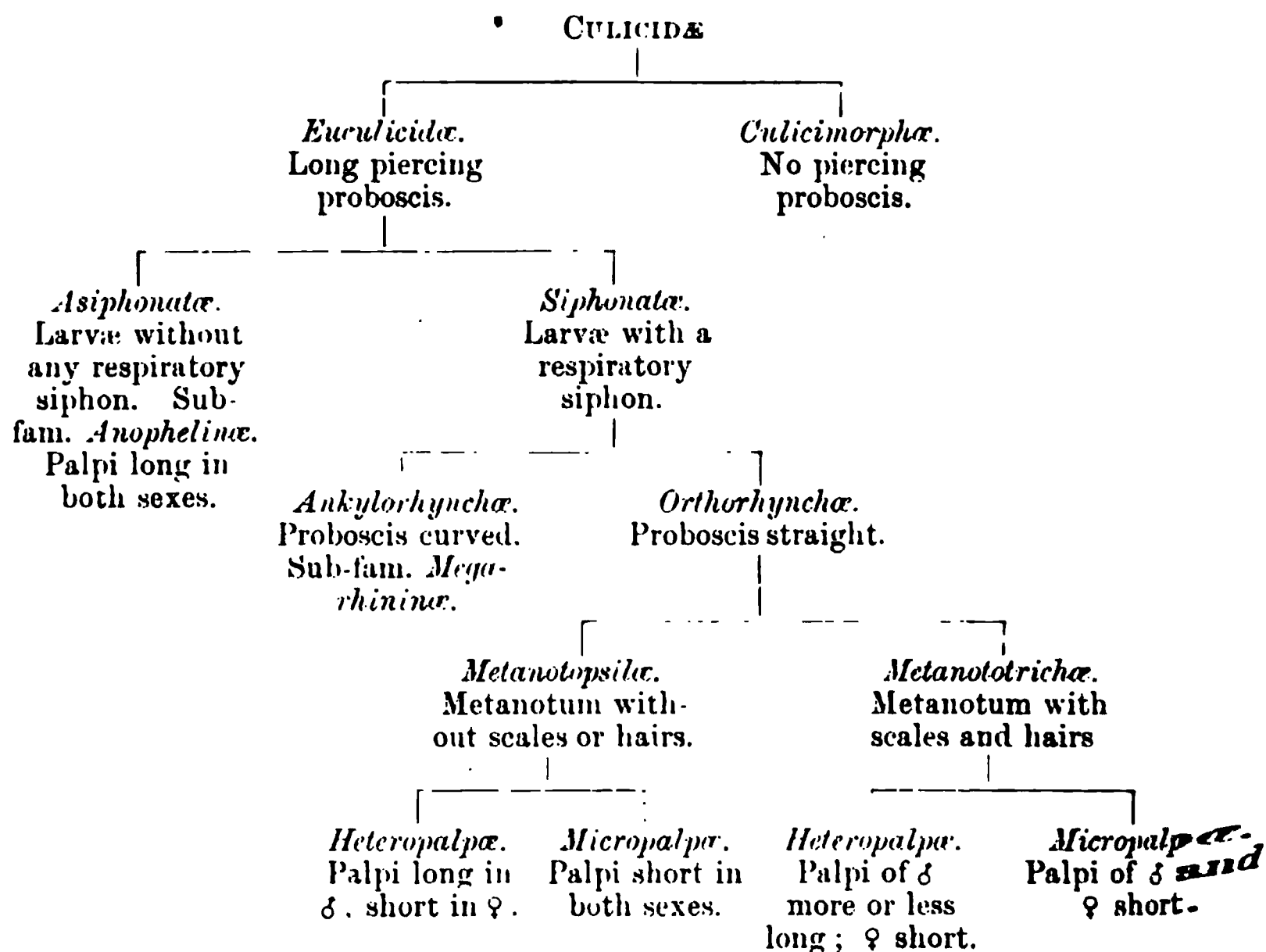
Palpi long in ♂, short in the ♀

Sub-fam. *Heptaphlebomyia*.

C. Proboscis not formed for piercing; with six long veins clothed with hairs, not scales

Sub-fam. *Corethrina*.

More recently Lutz has formulated a new general classification which is certainly satisfactory. In this he includes the old genera *Mochlonyx* and *Corethra*. These I exclude and place in a separate family—the *Corethridæ* (*Culicimorphæ* of Lutz).

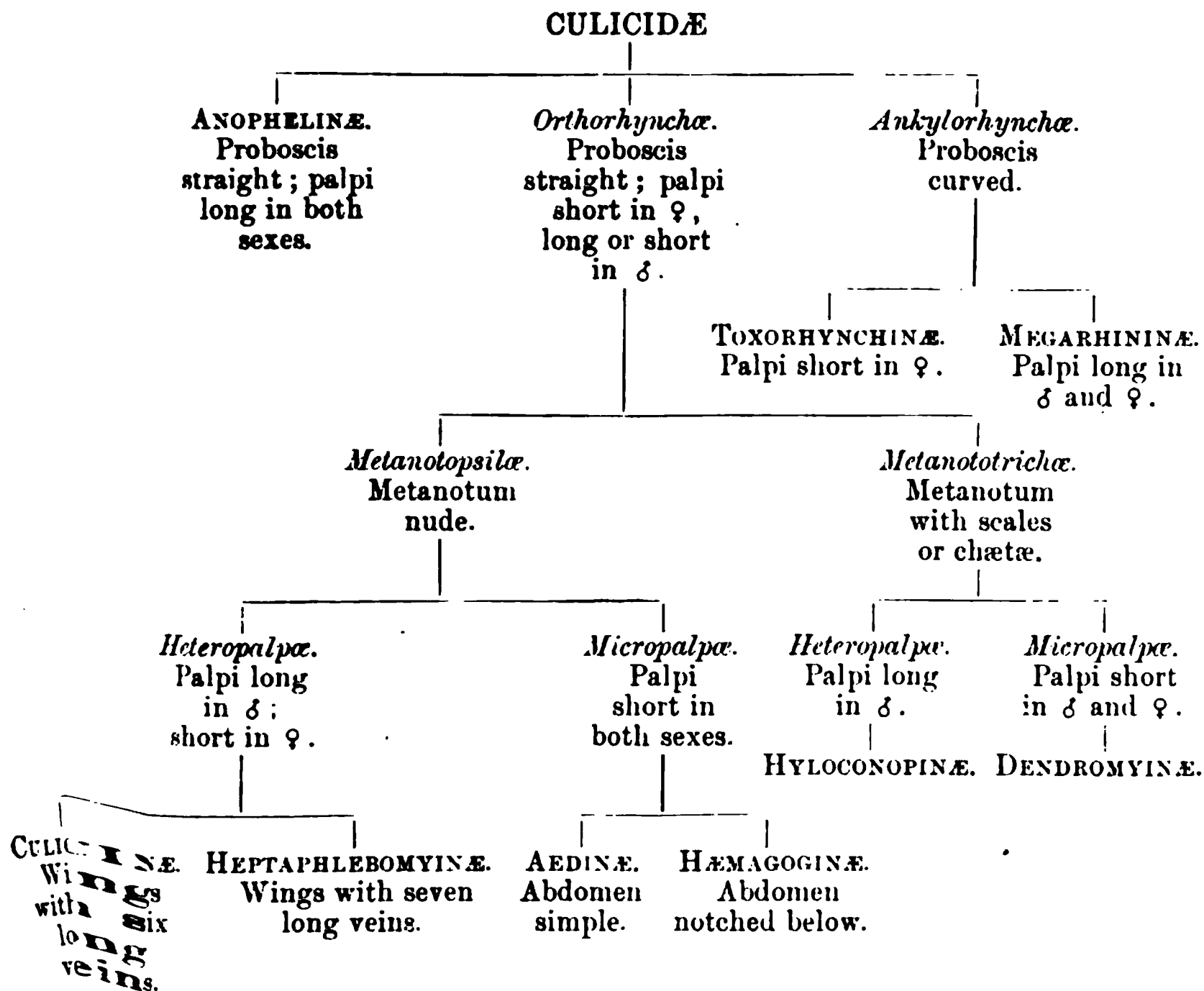


The *Asiphonata* = Sub-family *Anophelina*.

The *Siphonata* = { *Ankylorhynchæ* = Sub-fam. *Megarhinina*.  
*Orthorhynchæ* = 1. *Metanotopsilæ*. 2. *Metanototrichæ*.  
*Metanotopsilæ* { *Heteropalpæ*.  
*Micropalpæ*.  
*Heteropalpæ* = Sub-fam. *Culicina*.  
Sub-fam. *Heptaphlebomyina*.  
*Micropalpæ* = Sub-fam. *Aedina*.  
Sub-fam. *Hæmogogina*.  
*Metanototrichæ* { *Heteropalpæ*.  
*Micropalpæ*.  
*Heteropalpæ* = Sub-fam. *Hyloconopina*.  
*Micropalpæ* = Sub-fam. *Dendromyina*.

Lutz's *Culicimorphæ* should undoubtedly be excluded from the *Culicidæ*, and be known as a separate family—*Corethridæ*.

The best modification that can be made of this classification is as follows :—



This classification is thus based on the adult characters only, which is better than including larval characters as is done by Lutz. The generic characters are all formed by the structure and arrangement of the scales on the head, body, legs, and wings.



## LIST OF GENERA

## ANOPHELINÆ (Theobald)

- Genus 1. *Anopheles* (Meigen).  
 „ 2. *Myzomyia* (Blanchard).  
 „ 3. *Cyclolepteron* (Theobald).  
 „ 4. *Stethomyia* (Theobald).  
 „ 5. *Pyretophorus* (Blanchard).  
 „ 6. *Arribalzagia* (Theobald).  
 „ 7. *Myzorhynchus* (Blanchard).  
 „ 8. *Christya* (Theobald).  
 „ 9. *Lophoscelomyia* (Theobald).  
 „ 10. *Nyssorhynchus* (Blanchard).  
 „ 11. *Cellia* (Theobald).  
 „ 12. *Aldrichia* (Theobald).  
 „ 13. *Kertészia* (Theobald).  
 „ 14. *Bironella* (Theobald).  
 „ 15. *Neocellia* (Theobald).  
 „ 16. *Myzorhynchella* (Theobald).

## ANKYLORHYNCHÆ (Lutz)

A. *Toxorhynchinæ* (Theobald).

- Genus 17. *Toxorhynchites* (Theobald).

B. *Megarhininæ* (Theobald).

- „ 18. *Megarhinus* (Fabricius).  
 „ 19. *Ankylorhynchus* (Lutz).

*Orthorhynchæ—Metanotopsilæ*

## CULICINÆ (Theobald)

- Genus 20. *Theobaldia* (Blanchard).  
 „ 21. *Lutzia* (Theobald).  
 „ 22. *Mucidus* (Theobald).  
 „ 23. *Mansonia* (Blanchard).  
 „ 24. *Tæniorhynchus* (Arribálzaga).  
 „ 25. *Melanoconion* (Theobald).  
 „ 26. *Grabhamia* (Theobald).  
 „ 27. *Pseudograbhamia* (Theobald).  
 „ 28. *Acartomyia* (Theobald).  
 „ 29. *Psorophora* (Desvoidy).  
 „ 30. *Janthinosoma* (Arribálzaga).  
 „ 31. *Desvoidea* (Blanchard).  
 „ 32. *Eretmapodites* (Theobald).  
 „ 33. *Stegomyia* (Theobald).  
 „ 34. *Pseudoskusea* (Theobald).  
 „ 35. *Scutomyia* (Theobald).  
 „ 36. *Ædimorphus* (Theobald).

- Genus 37. *Leicesteria* (Theobald).  
 „ 38. *Macleaya* (Theobald).  
 „ 39. *Hulecotomyia* (Theobald).  
 „ 40. *Phagomyia* (Theobald).  
 „ 41. *Polyleptomyia* (Theobald).  
 „ 42. *Howardina* (Theobald).  
 „ 43. *Danielsia* (Theobald).  
 „ 44. *Lepidotomyia* (Theobald).  
 „ 45. *Catageiomyia* (Theobald).  
 „ 46. *Finlaya* (Theobald).  
 „ 47. *Trichorhynchus* (Theobald).  
 „ 48. *Quasistegomyia* (Theobald).  
 „ 49. *Bancroftia* (Lutz).  
 „ 50. *Culex* (Linnæus).  
 „ 51. *Lophoceratomyia* (Theobald).  
 „ 52. *Trichopronomyia* (Theobald).  
 „ 53. *Lasioconops* (Theobald).  
 „ 54. *Gilesia* (Theobald).

## HEPTAPHLEBOMYINÆ (Theobald)

- Genus 55. *Heptaphlebomyia* (Theobald).

## HÆMAGOGINÆ (Theobald)

- Genus 56. *Hæmagogus* (Williston).  
 „ 57. *Gualteria* (Lutz).

## AEDINÆ (Theobald)

- Genus 58. *Aedes* (Meigen).  
 „ 59. *Aedinus* (Lutz).  
 „ 60. *Aedeomyia* (Theobald).  
 „ 61. *Deinocerites* (Theobald).  
 „ 62. *Mimomyia* (Theobald).  
 „ 63. *Uranotænia* (Arribálzaga).  
 „ 64. *Anisocheleomyia* (Theobald).  
 „ 65. *Ficalbia* (Theobald).  
 „ 66. *Leptosomatomyia* (Theobald).  
 „ 67. *Polylepidomyia* (Theobald).  
 „ 68. *Verrallina* (Theobald).  
 „ 69. *Rhachionotomyia* (Theobald).  
 „ 70. *Etorleptomyia* (Theobald).

*Orthorhynchæ*—*Metanototrichæ*

## HYLOCONOPINÆ (Lutz)

- Genus 71. *Trichoprosopon* (Theobald).  
 „ 72. *Joblotia* (Blanchard).  
 „ 73. *Gældia* (Theobald).  
 „ 74. *Runchomyia* (Theobald).  
 „ 75. *Hyloconops* (Lutz).

## DENDROMYINÆ (Lutz)

- Genus 76. *Dendromyia* (Theobald).  
 „ 77. *Wyeomyia* (Theobald).  
 „ 78. *Phoniomyia* (Theobald).  
 „ 79. *Sabethes* (Desvoidy).  
 „ 80. *Sabethoides* (Theobald).  
 „ 81. *Sabethinus* (Lutz).  
 „ 82. *Limatus* (Theobald).

Of these genera the only ones that are known to be of medical interest at present are *Anopheles* (Meigen), *Myzomyia* (Blanchard), *Pyrethrophorus* (Blanchard), *Myzorhynchus* (Blanchard), *Nyssorhynchus* (Blanchard), *Cellia* (Theobald), *Stegomyia* (Theobald), and *Culex* (Linnæus). All the other Anopheline genera may probably be connected with malaria, and the Culicine *Mansonias* and *Tæniorhynchus* with filariasis. So far no disease has been traced to the *Ankylorhynchæ*, nor to the *Micropalpus*, *Metanotopsilæ*, nor any of the *Metanototrichæ*. A few of the more important genera in the latter only are mentioned here. For study of the other genera the reader is referred to my *Monograph of the Culicidæ of the World* (20). (Many new genera appear in Vol. IV.)

## The Anophelinæ

The Anophelinæ may be told from other Culicidæ by the combined characters of the long palpi in both sexes, the total absence of flat thoracic and scutellar scales, and their straight proboscis. Most have spotted wings, and when stationary are at an angle to the resting surface, the head, thorax, and abdomen being in one line; but an exception is found in *Myzomyia culicifacies* Giles in the latter habit, and some, as *A. bifurcatus* Linnæus and *Stethomyia nimba* Theobald, etc., in the former. The larvæ of all Anophelines have no respiratory siphon, and when at the surface of the water they lie nearly parallel with it.

Many are purely sylvan, and are responsible for bush fevers; some are entirely domesticated, as *Anopheles maculipennis*. There are at present known to be one hundred and three species, but this number will probably be gradually increased as further investigations are made.<sup>1</sup> At the same time it may be mentioned that some two dozen of the one hundred odd known species may probably turn out to be merely varieties.

Most species have spotted wings; too much importance has been attached to the distribution and pattern of the spotting, for we now know that there is a considerable amount of local and seasonal variation in the markings of the sub-family. The existence of several species has also been founded on combined wing and leg markings. Species related to *Myzorhynchus barbirostris* have been separated because the hind legs have one or more white hind tarsals, and also species near *Nyssorhynchus maculatus*; but as we know there is variation in this respect, it is quite possible that this leg banding will also prove to be a local and seasonal

<sup>1</sup> Since this went to press twelve new species have been described.

Variation. Certain collectors with no knowledge of insect life have also laid stress on the pale bands on the palpi, but these also vary, and cannot be accepted as valid characters.

The larval characters of chætotactic nature must be taken with great care, as we do not know whether the observers who have worked at this subject have been careful to examine all stages of the larvæ. Where we have checked them they have not always proved correct.

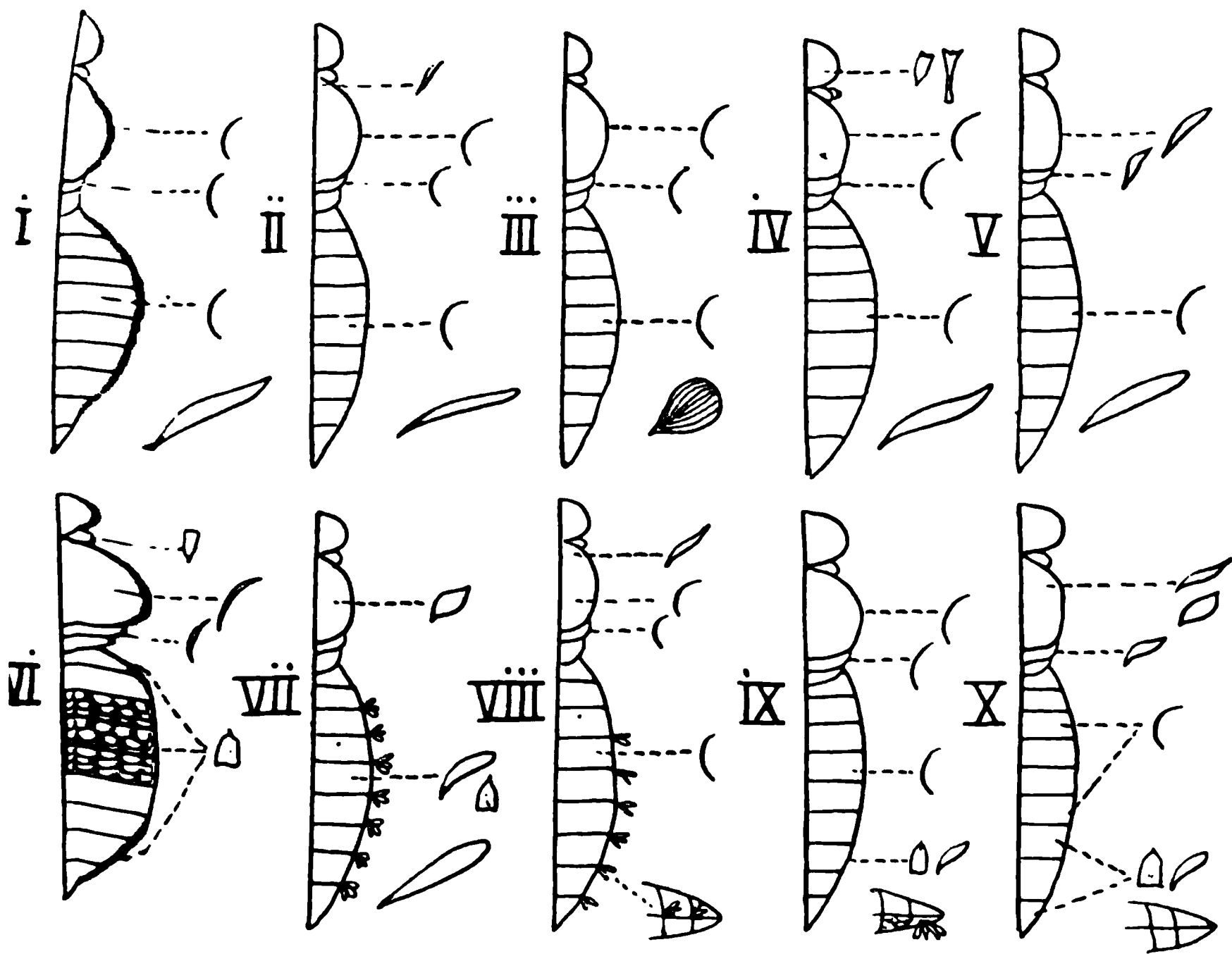


FIG. 145.—Squamose Characters of Anophelinae. i. *Anopheles*; ii. *Myzomyia*; iii. *Cyclolepteron*; iv. *Stethomyia*; v. *Pyretophorus*; vi. *Aldrichia*; vii. *Cellia*; viii. *Arribalzagia*; ix. *Myzorhynchus*; x. *Nyssorhynchus*.

The Anophelinae can best be divided into smaller groups or genera by scale structure, and accordingly the sub-family is split into the following groups, which may be tabulated as follows: <sup>1</sup>—

Sub-family ANOPHELINÆ.—In this sub-family the head has numerous upright-forked scales, rarely those of other form (*Stethomyia*). The thorax is scaly or hairy, the metanotum always nude, the scutellum always simple (never trilobed as in other Culicidæ), with scales or hairs. The abdomen is hairy, or scaly, in one genus (*Aldrichia*) as completely

<sup>1</sup> It may be pointed out here that these characters are adopted by all those who have worked scientifically at the Culicidæ, such as Lutz, Goeldi, Leicester, Felt, Blanchard, Barnard, Ludlow, Graham, Ventrillon, and all the other describers of valid species. Two medical observers, James and Liston, have discarded it.

scaled as in Culicinæ, etc. The palpi of the male are long and clavate, in the female long (usually as long as the proboscis), and of more or less uniform size throughout. With the exception of *Bironella*, the wings have all long fork-cells, the first sub-marginal longer than the second posterior cell. The ungues of the females always equal and simple, in the males the fore and mid are unequal, and may be uni-, bi-, or tri-dentate.

Taking the squamose structure of the thorax and abdomen, etc., we can tabulate the genera as follows:—

A. Fork-cells long.

a. Thorax and abdomen with hair-like curved scales.

α. Head with upright-forked scales only.

1. Wing-scales large and lanceolate, wing unspotted, or if spotted the spots due to collections of similar coloured scales

Genus *Anopheles* Meig.

2. Wing-scales small, narrowly lanceolate, the wings with spotting of varied colour . . . . . Genus *Myzomyia* Bl.

3. Wings with patches of large inflated scales

Genus *Cyclolepteron* Theo.

β. Median area of head with some flat scales

Genus *Stethomyia* Theo.

b. Thorax with narrow-curved scales, abdomen hairy.

Wing-scales small and lanceolate . . . . . Genus *Pyretophorus* Bl.

c. Thorax with hair-like curved scales and some narrow-curved ones in front; abdomen with apical lateral scale-tufts and scaly venter; no ventral tuft; wing-scales lanceolate . . . . . Genus *Arribalzagia* Theo.

d. Thorax with hair-like curved scales; no lateral abdominal tufts; a distinct apical ventral tuft and dense scaled palpi in the ♀.

Wings with dense, large, lanceolate scales

Genus *Myzorhynchus* Bl.

e. Thorax with hair-like curved scales and some narrow-curved lateral ones; abdomen hairy, with dense long hair-like lateral apical scaly tufts.

Wing-scales short and dense, lanceolate; fork-cells rather short

Genus *Christya* Theo.

f. Thorax with very long hair-like curved scales; abdomen with hairs except the last two segments, which are scaly; dense scale-tufts to hind femora.

Wings with broadish, blunt, lanceolate scales

Genus *Lophoscelomyia* Theo.

g. Thorax and abdomen with scales.

Thoracic scales narrow-curved or spindle-shaped; abdominal scales as lateral tufts and small dorsal patches of flat scales

Genus *Nyssorhynchus* Bl.

Abdomen nearly completely scaled with long irregular scales and with lateral scale tufts . . . . . Genus *Cellia* Theo.

Abdomen completely scaled with large flat scales as in *Culex*

Genus *Aldrichia* Theo.

B. Fork-cells very small, resembling those of *Uranotaenia* in form.

Body and thorax non-scaly . . . . . Genus *Bironella* Theo.

Genus *ANOPHELES*. Meigen, *Syst. Besch. Eur. zweifl. Ins. Dipt.* vol. 1. p. 10. 1818. — This genus is found in Europe, Northern Africa, in the hill districts of India, in Australia, the West Indies, North America, and one in West Africa. It is essentially a temperate region genus, those that occur in warm climates mostly occur in hill regions, but not all may have perfectly clear wings, and so might be mistaken for *Culicines*.

Fifteen species occur in the genus, the type of which is *Anopheles maculipennis*, common to Europe and North America. There are two unspotted winged European species, *A. bifurcatus* Linn., and *A. nigripes* Stenger, closely related forms to the first of these occur in Africa (*A. algeriensis* Theobald) and in Australia (*A. australiensis* Theobald); the type also occurs in North America, where a variety (*A. barberi* Coquillett) is evidently the same. Spotted winged forms occur, but the spotting is very scanty (*A. crucians* Wiedemann, *A. agas* Giles, etc.).

Some of this genus, such as *A. maculipennis* and *A. algeriensis*, are proved carriers of the malarial *Hæmaphysidæ*. The larvæ of *maculipennis* occur in pools and run water barrels; others, as *bifurcatus*, *agas*, and *lindsayi*, in small natural collections of water.

They may, as in *A. lindsayi*, occur high up in the hills in India. The adults (*maculipennis*) or larvæ (*bifurcatus*) may hibernate. Some are domesticated, others are found in the open country, and do not enter houses as a rule. Probably all can act as the hosts of the malarial parasites.

Genus *MYZOMYIA*. Blanchard, *C. r. Soc. biol. Paris*, vol. xxiii. p. 795, 1902. Some twenty-one species occur in this genus. The wings are all much spotted with areas of different coloured scales, and have more or less definite marks along the costa. They are mostly small mosquitoes. The type may be taken as the *Anopheles funesta* of Giles, which bears no resemblance to a true *Anopheles* whatever.

These mosquitoes are of varied habits. Some breed in pools and artificial collections of water (*M. rossii*), others in rivers and streams (*M. listoni* and *M. nili* and *M. funesta*). Five at least are proved malaria bearers, namely, *M. listoni* Liston and *M. funesta* Giles, *M. tuckhudi* Liston, *M. culicifacies* Giles, and probably *M. nili* Theobald. So far *M. rossii* Giles has been found incapable of transmitting the disease. One species (*M. culicifacies* Giles, ♀ non ♂<sup>1</sup>) rests in *Culicine* fashion. Some species are purely wild, such as *Myzomyia leucosphysa* Donitz and *M. elegans* James, whilst others, as *M. punctulata* Donitz and *M. rossii* Giles, come into houses. The genus has representatives in Europe (*M. superpicata* Grassi), in Africa (*M. funesta* Giles), Asia (*M. rossii* Giles), but not in South America, North America, the West Indies, or Australia.

<sup>1</sup> Giles' male of this was a different species (*M. tuckhudi* Liston)

The following are the known species :—

1. *M. funesta*. Giles, *Mono. Culicid.* i. p. iii. Central and Western Africa, Sudan, Philippine Islands. (Type.)
2. *M. rossii*. Giles, *Journ. Trop. Med.* 1899. India, Malay States, Philippine Islands.
3. *M. ludlowii*. Theobald, *Mon. Culic.* iii. p. 42, 1903. Philippine Islands, Malay.
4. *M. rhodesiensis*. Theobald, *ibid.* i. p. 184, 1901. Central Africa.
5. *M. culicifacies*. Giles (♀, non ♂), *Ent. Mon. Mag.* p. 197, 1901. India, Central Provinces, Berar, Madras.
6. *M. listonii*. Liston, *Ind. Med. Gaz.* 86, p. 12, 1901. India, Federated Malay States.
7. *M. longipalpis*. Theobald, *Mon. Culic.* iii. p. 37, 1903. British Central Africa.
8. *M. leptomeres*. Theobald, *ibid.* iii. p. 38, 1903. India.
9. *M. lutzii*. Theobald, *ibid.* i. p. 177, 1901. Brazil and British Guiana.
10. *M. turkhudii*. Liston, *Ind. Med. Gaz.* p. 441, 1901. India.
11. *M. hispaniola*. Theobald, *Mon. Culic.* iii. p. 49, 1903. Spain, Teneriffe.
12. *M. elegans*. James and Theobald, *ibid.* iii. p. 51, 1903. Bombay Presidency.
13. *M. punctulata*. Dönitz, *Ins. Börse*, 5. 18. 31. p. 37, 1901. Sumatra, Borneo, New Guinea.
14. *M. tessellata*. Theobald, *Mon. Culic.* i. p. 175, 1901. Straits Settlements.
15. *M. leucosphyra*. Dönitz, *Ins. Börse*, 5. p. 37, 1901. Sumatra, Borneo, New Guinea.
16. *M. albirostris*. Theobald, *Mon. Culic.* iii. p. 24, 1903. Malay States.
17. *M. nili*. Theobald, *First Rep. Gord. Coll. Well. Lab. Sudan*, p. 66, 1904. Sudan.
18. *M. thorntonii*. Ludlow, *Canad. Ento.* p. 69, 1904. Philippine Islands.
19. *M. aconita*. Dönitz, *Beit. z. d. Anop.* p. 70, 1902. Sumatra, Java.
20. *M. hebes*. Dönitz, *ibid.* p. 84, 1902. Dar-es-Salam, East Africa.
21. *M. pyretophoroides*. Theobald, *Mono. Culic.* iv. p. 48, 1906.

Genus CYCLOLEPPTERON. Theobald, *Mono. Culic.* vol. ii. p. 312, 1901.—Only two species occur in this genus—one (*C. grabhamia*, Theobald, *Mono. Culic.* i. p. 28, and iii. p. 56) from Jamaica, the other from Brazil (*C. mediopunctata*, Theobald, *Mono. Culic.* iii. p. 60). The members of this genus can at once be told by the patches of large inflated dark scales on the wings.

Genus STETHOMYIA. Theobald, *Journ. Trop. Med.* vol. v. p. 181, 1902.—This genus also contains but two species—one, *S. nimba* Theobald, from South America (*Mono. Culic.* iii. p. 62, 1903); the other, *S. fragilis* Theobald, from the Federated Malay States (*The Entomo.* p. 257, 1903). The main distinguishing feature is the presence of flat scales on the middle line of the head and hairy thorax and abdomen. The former species is probably connected with bush malaria in South America, and bites very viciously.

Genus PYRETOPHORUS. Blanchard, *C. r. Soc. biol. Paris*, No. 23, 795, 1902.—This is a large genus which so far only occurs in Africa, Asia, and Australia. It comes near *Myzomyia*, but can at once be told by having narrow-curved thoracic scales. They are also much larger than *Myzomyia*, and have prominently spotted wings. The larvæ are found in swamps and streams, and also in flowing water, in rice fields, and in rock pools.

Three species at least are connected with malaria, viz., *costalis* Loew, *chaudoyei* Theobald, and *ardensis* Theobald, all from Africa. It is essentially an African genus, but it also occurs in India, South America, and Australia. Eleven<sup>1</sup> species are known, as follows:—

1. *P. costalis* Loew, *Ent. Zeit. Berl.* p. 55, 1866. Africa and Mauritius. (Type.)
2. *P. marshallii* Theobald, *Mono. Culic.* iii. p. 77, 1903. Mashonaland.
3. *P. minimus* Theobald, *ibid.* i. p. 186, 1901. Hong Kong.
4. *P. ardensis* Theobald, *Journ. Econ. Biol.* i. p. 17, 1905. Natal.
5. *P. chaudoyei* Theobald, *Mono. Culic.* iii. p. 68, 1903. Algeria.
6. *P. superpictus* Grassi, *Rea. Acad. Linc. (Stud. Zool. s. Malaria)*, p. 78, 1900. S. Europe.
7. *P. palestinesis* Theobald, *Mono. Culic.* iii. p. 71, 1903. Palestine, Syria, and Persia.
8. *P. jeypurensis* Theobald, *ibid.* iii. p. 66, 1903. India.
9. *P. cinereus* Theobald, *ibid.* i. p. 161, 1901. S., W., and Central Africa.
10. *P. atratipes* Skuse, *Proc. Linn. Soc. N. S. Wales*, iii. p. 1755. New South Wales, Queensland.
11. *P. lutzii* Cruz, *Mosquitos do Brasil*, p. 19, 1904.

Genus ARRIBÁLZAGIA. Theobald, *Mono. Culic.* iii. p. 81, 1902.—A single species only occurs in this genus at present. It can be told from the other genera by having hair-like curved scales all over the thorax and abdomen, except for a few narrow-curved ones in front of the thorax, and a lateral abdominal scale-tuft and scaly venter; otherwise it comes near the next genus (*Myzorhynchus*). The single species (*A. maculipes* Theobald, *Mono. Culic.* iii. p. 81, 1903) occurs in the Brazils and in Argentina, and is said to be a malaria-carrier.

Genus MYZORHYNCHUS. Blanchard, *C. r. Soc. biol.* v. 23. p. 795, 1902.—This very marked genus can at once be told by its densely scaly palpi; the thorax with hairs; abdomen, except the last few segments, with hairs and a ventral apical scale-tuft. (There are no lateral tufts as in the former genus.) The proboscis is densely scaly. They are mostly large and dark species, but may have much white on the legs. All known at present are wild insects, and breed, as a rule, in swampy places, especially dark pools with much vegetation and water overgrown with green weeds. They are vicious biters, and several are probably connected with malaria, although nothing has been definitely proved so far. The malarial parasites can, however, develop in them,

<sup>1</sup> Twenty-six species are now known. (*Vide* Vol. IV. "Mono. Culicidæ.")



and it is probable that they account for malaria contracted in the open. So far none seem to occur in houses. All the larvæ have much branched, almost brush-like, frontal hairs. One species (*M. nigerrimus*) has been found to prove an efficient host for *Filaria bancrofti*. The genus occurs in Africa, Asia, S. Europe, and Australia.

The following species are known :—

1. *M. barbirostris*. Van der Wulp, *Leyd. Mus. Notes*, 6. p. 48. India, West Africa. (Type.)
2. *M. bancrofti*. Giles, *Hbk. Gnats*, 2nd ed. p. 511, 1902. Queensland.
3. *M. umbrosus*. Theobald, *Mono. Culic.* iii. p. 87, 1903. Malay.
4. *M. albotæniatus*. Theobald, *ibid.* iii. p. 88, 1903. Straits Settlements.
5. *M. sinensis*. Wiedemann, *Ausseuro. Zweit. Ins.* p. 547, 1828. China, Formosa; Federated Malay States.
6. *M. vanus*. Walker, *Journ. Pro. Linn. Soc.* v. p. 91, 1860. Malay, China.
7. *M. annularis*. Van der Wulp, *Leyd. Mus. Notes*, 9. p. 249, 1889. East Java, Malay, India.
8. *M. pseudopictus*. Grassi, *Rea. Acad. Linc. (Stud. Zool. S. Malaria, 1890)*. Italy.
9. *M. minutus*. Theobald, *Mono. Culic.* iii. p. 91, 1903. India (Punjab).
10. *M. nigerrimus*. Giles, *Hbk. Gnats*, p. 161, 1900. India.
11. *M. mauritanus*. Grandpré and Charmoy, *Les Moustiques, Planters' Gazette*, 1900. Mauritius, Central and Northern Africa.
12. *M. plumiger*. Dönitz, *Ins. Börse*, Jan. 1901. Hong Kong, East India.
13. *M. paludis*. Theobald, *Report Mal. Com. Roy. Soc.* p. 75, 1900. West, Central, and Northern Africa.
14. *M. pseudobarbirostris*. Ludlow, *Journ. N. York Ent. Soc.*, Sept. 1902. Philippine Islands.
15. *M. coustanii*. Laveran, *Arch. d. Parasit.* 6. p. 389, 1902. Madagascar.
16. *Strachanii*. Theobald, *Mono. Culic.* iv. p. 85, 1906.

Genus *CHRISTYA*. Theobald, "Rep. Sleeping Sickness," *Royal Soc.* vol. vii. p. 84, 1903.—A single species only occurs in this genus, which is allied to the former, but can easily be told by the *very long lateral apical tufts of scales on the abdomen*. The fork-cells are rather short, and the thorax has hair-like scales, with narrow-curved ones laterally, and the prothoracic lobes with narrow-curved scales. The single species (*C. implexa*, Theobald, "Rep. Sleeping Sickness," *Roy. Soc.* vol. vii. p. 84, 1903) comes from Uganda.

Genus *LOPHOSCELOMYIA*. Theobald, *The Entomologist*, p. 12, 1904.—This genus is so far only known in Malaya. The head has narrow-curved as well as upright-forked scales; palpi densely scaled. Thorax with long curved hair-like scales, prothoracic lobes with a tuft of spatulate scales. The legs have dense tufts of outstanding scales at the apex of the hind femora.

The larvæ of the only species (*L. asiatica*, Leicester, *Entomo.* p. 13, 1904) live in the water collected in pierced and fallen bamboos in the Malay jungles.

Genus NYSSORHYNCHUS. Blanchard, *C. r. Soc. biol.* vol. xxiii. p. 795, 1902.—A number of species occur in this group. Some are malaria-bearers, or at least the parasites may develop in them (*N. stephensii*, etc.). This is a very marked genus, but contains a few aberrant forms.

The thorax has narrow-curved and spindle-shaped scales. The abdomen has scales on the venter and dorsal patches mostly on the apical segments. Many have spotted legs and one or more white hind tarsals, which undoubtedly vary in number at different seasons, as also do the wings and palpal banding. The species are all best distinguished by squamose characters which do not vary in form. The larvæ are mostly pot and puddle breeders; some, however, live in marshes, others in hill streams in jungles. The adults occur both in houses and huts and out of habitations.

Some dozen or more species are known. The following have been described :—

1. *N. maculatus*. Theobald, *Mono. Culic.* i. p. 171, 1901. India, Malay. (Type.)
2. *N. theobaldii*. Giles, *Ent. Mon. Mag.* p. 198, 1901. India, Aden Hinterland.
3. *N. stephensii*. Liston (= *metaboles* Theob.), *Ind. Med. Gaz.* 36. p. 12, Dec. 1901. India.
4. *N. fuliginosus*. Giles, *Hbk. Gnats*, p. 160, 1900. India, Fed. Malay States.
5. *N. maculipalpis*. Giles, *ibid.* 2nd ed. p. 297, 1902. India, Mauritius, and Mashonaland.
6. *N. pretoriensis*. Theobald, *Mono. Culic.* iii. p. 99, 1903. Pretoria; Natal.
7. *N. witmorii*. James, *ibid.* iii. p. 100, 1903. Kashmir, Malay.
8. *N. karwarii*. James, *ibid.* iii. p. 102, 1903. Karwar, Goa, and Malay.
9. *N. annulipes*. Walker, *Ins. Saund.* i. p. 433, 1850. Australia.
10. *N. masterii*. Skuse, *Proc. Linn. Soc. N. S. Wales*, p. 1757, 1889. Australia.
11. *N. nivipes*. Theobald, *The Entomo.* p. 258, 1903. Fed. Malay States.
12. *N. jamesii*. Theobald, *Mono. Culic.* i. p. 134, 1901. South India and Ceylon.
13. *N. philippinensis*. Ludlow, *Journ. N. York Ent. Soc.* x. p. 128, 1902. Philippine Islands.

Genus CELLIA. Theobald, *Mono. Culic.* vol. iii. p. 107, 1903.—The seven species of this genus all present similar characters, the most marked being the more or less densely scaled abdomen with dense lateral tufts; the abdominal scales may be longish narrow-curved ones or spindle-shaped; the thorax has many flat spindle-shaped scales, and the wings are densely scaled. The dense irregular abdominal scales are the most marked character. Two or three species prove efficient hosts for the malarial parasites (*C. pharoensis*; *C. argyrotarsis*, and probably *C. albimanus*).

The larvæ live in pools and water-courses, canals, roadside puddles, and any open water. Some, as *C. kochii*, are most abundant in the

vicinity of habitations. The adults, as seen in *C. pharoensis* and *C. pulcherrima*, are found in houses, barracks, and native huts.

The genus occurs in Asia, Africa, South America, and the West Indies. The following have been described :—

1. *C. pharoensis*. Theobald, *Mon. Culic.* i. p. 169, 1901. Africa (West, East, Central, and Northern). (Type.)
2. *C. pulcherrima*. Theobald, *Proc. Roy. Soc. Lond.* lxi. p. 369, 1902. India.
3. *C. squamosa*. Theobald, *Mon. Culic.* i. p. 167, 1901. Africa generally.
4. *C. kochii*. Dönitz, *Ins. Börse*, v. p. 18, Jan. 31, 1901. Federated Malay States, Sumatra, Java, Philippine Islands.
5. *C. argyrotarsis*. Robineau-Desvoidy, *Essai sur les Culicid*, p. 411, 1827. West Indies and South America and South of North America.
6. *C. albimanus*. Wiedemann, *Mon. Culic.* i. p. 125, 1901. West Indies, British Guiana, Brazil.
7. *C. bigotii*. Theobald, *Mono. Culic.* i. p. 135, 1901.

Genus ALDRICHIA. Theobald, *Mono. Culic.* iii. p. 353, 1903.—This is the most marked Anopheline genus, and can at once be told by the abdomen being completely covered with flat overlapping scales as in *Culex*. The thorax has narrow-curved, almost hair-like scales, and flat outstanding ones to the prothoracic lobes.

Nothing is known of the single species *A. error* (Theobald, *Mon. Culicid.* iii. p. 353, 1903), which was taken in India. The species was placed as *one of the types of Giles' rossii*!

Genus BIRONELLA. Theobald, *Ann. Mus. Nat. Hung.* iii. p. 69, 1905.—In this genus the mesothorax has numerous short curved hairs, abdomen nude and hairy, head with upright-forked scales of two kinds. The first fork-cell in the male is *very small*, with its stem at least four times the length of the cell, the second posterior much larger than the first sub-marginal cell. The most marked feature is the wing venation. The male only is known, and but a single species, *B. gracilis* Theobald (*Ann. Mus. Nat. Hung.* iii. p. 69, 1905), found in New Guinea.

#### GENUS UNCERTAIN

Some nineteen species (?) have been described in such a way that their generic position cannot be determined. Probably several of these are invalid species :—

- Anopheles martinii*. Laveran, *C. r. Soc. biol. Paris*, liv. p. 907, 1902.  
*A. antennatus*. Becker, *Mitt. ans. d. Zool. Mus. in Berlin*, ii. p. 68, 1903.  
*A. brachypus*. Dönitz, *Zeip. Hyg.* p. 52, 1903.  
*A. maculicostus*. Becker, *M. a. d. Zool. Mus.* ii. p. 69, 1903.  
*A. multicolor*. Cambonlin, *C. R. Acad. des Science*, cxxxvi. p. 704, 1902.  
*A. vincentii*. Laveran, *C. r. Soc. biol. Paris*, liii. p. 993, 1901. Tonkin.  
*A. farautii*. Laveran, *ibid.* liv. p. 908, 1902. New Hebrides.  
*A. pursatii*. Laveran, *ibid.* p. 906. Cambodia.

- A. patus*. Loew, *Inpt. Beitr.* p. 4, 1845.  
*A. Nyssorhynchus* (?) *deceptor*. Donitz, *Zeitschr. f. Hyg.* xl. 1903.  
*A. Myzomyia* (?) *impunctus*. Donitz, *ibid.*  
*A. Pyretophorus* (?) *nerus*. Donitz, *ibid.* p. 77.  
*A. annulimanus*. Van der Wulp, *Tijdsch. v. Entomo.* x. p. 130, 1867.  
*A. annulipalpis*. Airibalzaga, *Naturalista Argent.* p. 149. 1 1878.  
*A. Myzorchychnus* (?) *ziemannii*. Grunberg, *Zool. Anzeiger*, xxv p. 677, 1902.  
*A. Anopheles* (?) *eisemi*. Coquillett, *Journ. N. Y. Ent. Soc.* x p. 192, 1902.

Colonel Giles also describes a damaged species as *A. patchfordii* from Zululand that is not valid (*Revision of Anophelinae*, p. 34. 4. 1904).

#### CULICINÆ

The Culicinae are those mosquitoes which have a straight proboscis. short palpi in the females, long in the males, the metanotum is nude, and they have only six scaled longitudinal veins.

There are thirty-five very distinct genera, which can easily be distinguished by the squamose ornamentation of the head, thorax, legs, and wings.

In this important group comes the yellow fever bearer, *Stegomyia* *proctori*, and true *Culex*, which are intimately connected with filariasis.

There are several genera (*Muculops*, *Scutomyia*, etc.) closely related to *Stegomyia*, but at present none have been found to be connected with disease.

The old genus *Culex* contained all manner of diverse forms, but has been recently divided into many genera, squamose characters again being found to be the only trustworthy ones.<sup>1</sup>

All the larvæ have long siphons, but there is considerable variation in regard to general length in many of the genera. As a rule each genus has sylvan and domestic species. The larvæ are found in all manner of collections of water, several (*Muculus* spp., *Culex marinus*, etc.) can live in the sea and even brine pools. The most important genera are mentioned here, the reader being referred to my monograph (20) for farther details.

Genus THEOBALDIA NEVEU-LEMAIRE.—The members of this genus are often confused with the true *Anopheles* because the wings are frequently spotted with dark groups of scales, which may or may not be very pronounced. The type is *T. annulata* Schrank, which bears a superficial resemblance to *Anopheles maculipennis* Meigen, but can at once be told by its banded legs. The scales on the head (except the sides) are narrow curved and upright forked ones, those on the scutellum narrow curved. The palpi of the males are longer than the proboscis and clavate, those of the female prominent, but much shorter than the proboscis. The spotted wings, clavate male palps, and large lanceolate vein scales render them very distinct from other Culicines. The species

<sup>1</sup>Wied has made several new good genera out of *Culex* adopting 3 genitalic characters only, and these are found to agree with their separation on squamose characters alone.

belong to temperate climates, when they occur elsewhere they are usually found in hill regions, but recently *T. spathipalpis* Rondani has made its appearance at Khartoum and the Cape, and is found in abundance at Madeira and Teneriffe, and also in Algeria, Gibraltar, and Morocco. The six species are domestic, and hence are easily spread artificially by rail and boat. They all bite very viciously, and frequently cause nasty wounds at night, when they are most active. Two of the commonest species, *annulata* and *spathipalpis*, are of frequent occurrence in privies.

The larvæ have a short, rather thick siphon, and are found in rain-water barrels, etc. The adults hibernate during the winter in cellars, outhouses, and dark places. The males die off in the autumn after having fertilised the females.

The following species exist :—

1. *Theobaldia annulata*. Schrank, *Beitr. Natur.* p. 97. 70, 1776. Europe, India (Punjab), North America, and ? Mexico. (Type.)  
This is one of the worst biting British Culicines.
2. *Theobaldia ficalbii*, Noé, *Bull. Soc. Ent. Ital.* 31, p. 231, 1890. Italy.
3. *Theobaldia glaphyroptera*. Schiner, *Faun. Austr. Die Fliegen.* ii. p. 628, 10, 1864. Austria.
4. *Theobaldia incidens*. Thomson, *Eugen. Resa. Dipt.* p. 443. California and other parts of the U.S.A., New Mexico.
5. *Theobaldia spathipalpis*. Rondani, *Dipt. Ital. Pro.* vol. i. 1886. Italy, Mediterranean Islands, Gibraltar, Algeria, Morocco, Madeira, Canary Islands, Cape Colony, Sudan and Egypt, and India.  
A very vicious biter, frequently found in privies.
6. *Theobaldia penetrans*. Desvoidy, *Ess. Culic.*, 1827. France.

Genus *MUCIDUS* Theobald.—This genus is very peculiar, owing to the mouldy-looking appearance of the insects, which have long twisted outstanding grey scales on the head, thorax, legs, and abdomen. The legs have dense outstanding scales, and the wings are mottled and have broad pyriform or fan-shaped scales, which are parti-coloured. The larvæ live in both salt and fresh water, and are carnivorous, feeding upon the larvæ of other Culicids, even large *Toxorhynchus*, and in turn are preyed upon by them. They have long and thick siphons. The pupæ have short, broad air-trumpets, and no caudal fins. The adults bite viciously. Species occur in Africa (*M. africanus* Theobald, and *M. mucidus* Karsch), in Australia (*M. alternans* Westwood), and in India and the East Indies (*M. laniger* Wiedemann, and *M. scatophagoides* Theobald). So far no human disease has been connected with this genus.

Genus *MANSONIA* Blanchard.—This very marked genus can at once be told from other Culicinæ by the broad, flat, asymmetrical wing-scales, which are mottled. The females frequently occur in enormous numbers, and bite most viciously, producing great irritation. Swarms are found along the Nile, making life unbearable at twilight and at night. Representatives occur in Asia, Africa, North and South America, and Australia, but

the number of species is few (seven). The larvæ have a very distinct spoon, with a broad base and the apex much contracted, and the pupæ have the air trumpets long and curved irregularly. The ova are laid separately, and have long necks quite unlike those of any other Culicine.

Members of the genus may be connected with filarial diseases. One species (*M. uniformis* Theobald) occurs in Africa, India, and Australia (*M. africana* Theobald and the *australensis* Giles are this species).

Three species occur in South America, Southern North America, and the West Indies (*M. titillans* Walker, *M. pseudotitillans*, and *M. amazonensis* Theobald), three in Africa (*M. uniformis*, *M. major*, and *M. nipa* Theobald), and three in Asia (*M. uniformis*, *M. annulifera* Theobald, and *M. annulipes* Walker).

Genus *MELANOCONION* Theobald.—These are all very small black mosquitoes, some of them bite very viciously, and owing to their small size are able to get through ordinary mosquito curtains. The head and scutellum have small narrow-curved scales. The main difference from *Culex* is that the scales on the apical portions of the wings are small, short, dense, and broad, and also along the upper costal border, which has spine-like scales on the outer edge. The femora are swollen at their base and apex, and the tibiae at their apices.

They are both domestic and sylvan, the latter swarming in swamps and forests. The type is *M. atratus* Theobald, found in the West Indies and South America; three species occur in South America, three in the West Indies (*M. atratus*, *M. spaspes* Theobald, *Mono. Culic.* iii. p. 242; *M. neotropicus* Theobald, *ibid.* n. p. 322). The larvæ have a very long thin spoon, and the pupæ two long thin air-trumpets.

The larvæ occur in permanent pools, and neither minnows nor dragon-fly larvæ appear to destroy them, in spite of their delicate nature. They feed on algae, and are often green in colour.

Genus *GRABHAMIA* Theobald. Many of these are vicious biters, producing painful wounds. The head and thorax have narrow curved scales, the former somewhat broader than in *Culex*. The wings have rather thick median vein scales, and broadish short lateral ones on the subcostal veins and on the major areas of the upper ones; the scales, being black and yellow or white, give the wings a pepper and salt appearance, the fork cells are short, and the wings short and stumpy. The eggs are deposited singly, not in rafts, and may be laid on damp mud as well as in water. The larvæ have short, thick siphons, and in one species at least (*G. jamaicensis* Theobald) they lie parallel with the surface of the water, but somewhat bent in the middle.

At least fifteen species are known; the majority come from Europe and North America, one from Natal, and another from the Philippine Islands.

The type is *Grabhamia jamaicensis* Theobald (*Mono. Culic.* ii. p. 345, 1901), which occurs in North America and Jamaica.



*Grabhamia dorsalis* Meigen (*Syst. Besch. zweifl. Ins.* iv. p. 242, 1818) is the most abundant European species, and bites very ravenously at night, especially along the valley of the Thames and Medway and on the eastern coast of Britain. The larvæ breed in pools and dykes, and are found especially in those with muddy banks. The adults do not, as a

rule, occur indoors, but *G. spencerii* Theobald (*Mono. Culic.* ii. p. 280) is an indoor pest,—a variety (*idahoensis* Theobald) is so small that it readily crawls through ordinary mosquito nets.

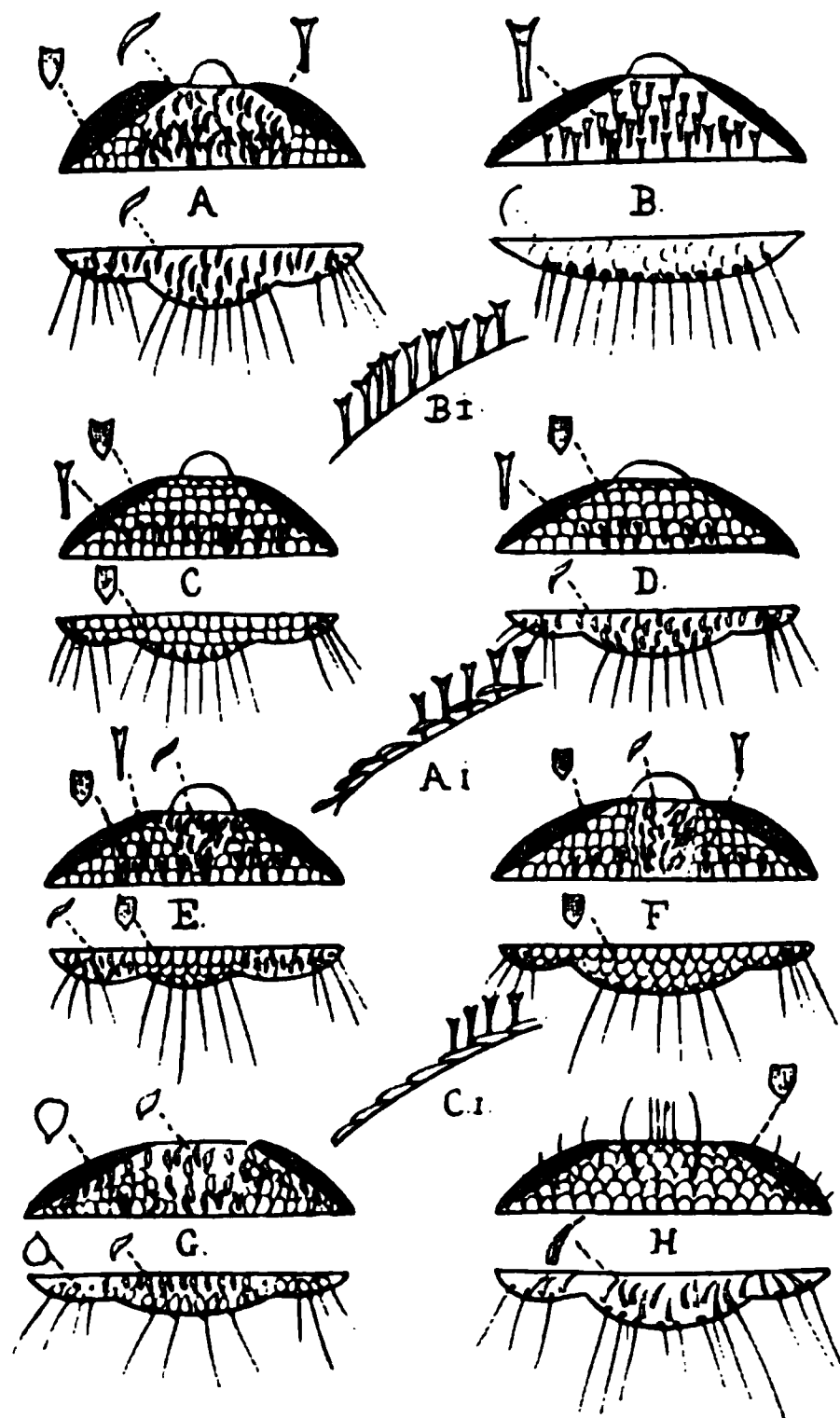


FIG. 96.—Cephalic and Scutellar Characters. A, *Culex*; B, *Anopheles*; C, *Stegomyia*; D, *Danielsia*; E, *Macleaya*; F, *Scutomyia*; G, *Finlaya*; H, *Mimomyia*. A<sub>1</sub>, B<sub>1</sub>, and C<sub>1</sub>, side views of A, B, and C.

Genus *STEGOMYIA* Theobald. After the *Anophelinae* the next most important group is *Stegomyia* and some allied genera.

This genus differs markedly from *Culex* in general appearance. The species are all small, dark insects with silvery markings, and many have their legs banded with white. They are often called Tiger Mosquitoes. The importance of the genus is that it contains the yellow-fever carrier, *Stegomyia fasciata*, at present the only species known to be implicated. There is, however, no reason to imagine that the others are not capable of transmitting the disease, so that their distribution is a matter of importance. The

characters of the genus are as follows:—Head entirely covered with flat scales and some upright-forked ones. The palpi of the female are short and small; in the male they are long and thick, with scanty hair-tufts. The thorax has narrow-curved, or almost spindle-shaped scales, except the scutellum, which has always dense flat scales. The combination of head and scutellar-scale structure are the main generic features. The wings have rather short fork-cells, and the scales are brown and dense, those on the apices of the veins especially so; they are broader than in a typical *Culex*. The ornamentation of the thorax is very variable, and most species can be identified by these markings alone.

Some are very vicious biters, and invade houses in great numbers ; others are mainly sylvan. They bite both by day and night. The larvæ have short thick siphons, and are found in barrels, cisterns, artificial pools, and even in such small collections of water as those found in jam-pots, calabashes, and empty sardine tins.

The ova are deposited singly, not in rafts, and are black and oval, surrounded with a series of small air-chambers. The ova can withstand long desiccation ; some of *S. fasciata* sent to me from Cuba hatched out—after having been left in a dry test-tube for two months—when placed in tepid water in less than twenty-four hours.

There are at present known to be seventeen species in this genus, which occurs in tropical, subtropical, and the warmer temperate regions only, roughly speaking to about 40° on each side of the equator. Seven species occur in Asia, six in Africa, two in Australia, two in North America, and one in the Philippine Islands. The following are the more important species :—

*Stegomyia fasciata* Fabricius.—This so-called Tiger Mosquito—the yellow-fever carrier—has been described under no less than eighteen different names. The reason for this is not always clear, as one authority (Walker) described it as seven separate insects. This species can at once be told by the thoracic adornment. The thorax and the whole ground colour of the insect is deep blackish-brown ; the thorax has two median parallel yellow scaled lines, and on each side of them a curved silvery white line ; the dark abdomen has a basal white band on each segment, and the black legs have basal white bands. Three distinct varieties occur ; one (the *Culex mosquito* of Arribáizaga) has no median parallel thoracic lines ; the second (*luciensis* Theobald) has the last hind tarsal all white ; and, thirdly, *queenslandensis* Theobald, in which the abdomen has basal and apical pale bands and many white scales over the whole abdominal surface. This insect was first described by Fabricius (*Syst. Antl.* 36. 13. 1805) as *Culex fasciatus*. It was raised to generic rank owing to scale-structure in 1901 (*Mono. Culic.* I. p. 283).

It breeds in all manner of places close to and in man's habitations, such as rain-water barrels, cisterns, tanks on steamers, water-jugs indoors, water collected in pots and pans, old sardine tins and calabashes, and when forced to in pools and dykes.

The Tiger Mosquito bites chiefly between the hours of 1 and 3 P.M., but also at night. It is attracted to dark colours, choosing such to rest upon, and attacks people dressed in dark clothes much more than those in pale garments.

It rests and shelters in curtain hangings, dark clothing, and corners of walls during the early part of the day. The males have been said to bite (Ficalbi), but this is not so. Both males and females feed upon bananas ; and in this way, having been attracted by them, they are carried during the transit of the fruit abroad.

The *distribution* is very wide ; the following are localities from which it has been recorded :—*Europe*—Southern Italy, Spain, Portugal, Greece,



Malta. *Asia*—Ceylon, Eastern Hindoostan, Malay Peninsula (certain ports, but not inland), Siam (one), Southern Japan, Palestine. *Africa*—West Coast, Senegambia, Freetown, Lagos, Nigeria, Old Calabar, Uganda, Sudan, and down the Nile into Egypt and along the Suez Canal, Gibraltar, Algeria, and Morocco. *Australia* generally, abundant in the uplands of Victoria, and in Queensland; at Port Darwin, South Australia. *Eastern Archipelago*—Java, Sumatra, British New Guinea. *South America*—British and French Guianas, down through the Brazils to the Argentine; Ecuador, Peru, Chile. In *Central America* at Panama, Costa Rica, British Honduras, Nicaragua, Guatemala, and in Mexico. *North America*—in Missouri, Indiana, North Carolina, Maryland, Arizona, South Carolina, Texas, Florida, Georgia, Alabama, Mississippi, Louisiana, Arkansas, Tennessee, Illinois, Kentucky, Virginia. *West Indies*—Jamaica, St. Lucia, Cuba, Haiti, Antigua, Grenadine Islands, Montserrat, Dominica, Barbados, Trinidad, Caymans, Nevis, St. Kitts, Bahamas. *Oceanic Islands*—Madeira and Teneriffe, Seychelles, Philippine Islands, Fiji, Samoa, Sandwich Islands, most of the South Pacific Islands (Pitcairn, etc.), St. Vincent.

*Stegomyia fasciata* readily travels by boat and train, and in this way its very wide distribution can be explained. Fortunately its breeding haunts are in and around man's habitations, and hence the larvæ can be stamped out more easily than in the case of the Anophelinæ. The beneficial results of destroying this insect have been seen in Havanna, where yellow fever has consequently ceased to be a scourge.

The *Asiatic Stegomyian* (*S. scutellaris* Walker).—This species is very closely related to *S. fasciata*, and resembles it in general shape and coloration; but it can at once be told by having *one* median silvery white line on the mesothorax. Its distribution is confined to Asia and some Oceanic Islands. The following are localities where it has been recorded:—Ceylon, Sombalpur, Central Provinces, Calcutta, Madras, Naini Tal, Canara district, Goa in India; Penang, Perak, Singapore, Selangor, Upper Burma, Kwala Lumpur in Malay; Siam, Christmas Island, Amboina, Celebes, North Borneo, British New Guinea in the East Indies; Hong Kong, Foo Chow, and Shaohyling in China; Formosa, Japan, Mauritius, Fiji, Victoria, Seychelles, Philippine Islands, Samoa. To these different islands it has probably travelled by boat.

Strictly speaking, this insect is a sylvan one. The larvæ are found in small dark holes, in wells, in hollow trees, in empty cocoa-nut shells, and in cut bamboos. They feed upon rotting leaves, and revel in the dark. Nevertheless they become domesticated in large numbers, especially where extensive growths of jungle and forest have been cleared for habitations, and may then be found breeding in tubs, water-jugs, cisterns, inside houses as well as in any receptacles of water inside. The bite is most irritating, and when they have once found out a person they will follow him out of the dark forest or jungle into the bright sunlight. As it is so closely related to the yellow-fever carrier its habits and distribution are of great importance, for there is no reason to doubt that

might not play the same rôle if yellow fever were introduced into Asia.

The other members of the genus are not so important, being neither abundant nor of such wide distribution. They are as follows:—

3. *Stegomyia africana*. Theobald, *Mon. Culic.* i. p. 304, 1901. West and Central Africa.
4. *Stegomyia thomsonii*. Theobald, *Genera Ins. Culic.* p. 18, 1905. N.W. Provinces, India.
5. *Stegomyia grantii*. Theobald, *Mon. Culic.* i. p. 306, 1901. Sokotra.
6. *Stegomyia nigeria*. Theobald, *idem*, i. p. 303. Bonny, West Africa.
7. *Stegomyia crassipes*. Van der Wulp, *Dipt. Mid. Sum.* p. 9. Burma and Soeroelangoen.
8. *Stegomyia argenteopunctata*. Theobald, *Mon. Culic.* v. p. 316, 1901. Mashonaland.
9. *Stegomyia punctolateralis*. Theobald, *Entomologist*, 36, p. 156, 1903. Queensland.
10. *Stegomyia signifer*. Coquillett, *Canad. Ento.* xxviii. p. 43, 1896. North America.
11. *Stegomyia amesii*. Ludlow, *Journ. N. York Ent. Soc.* p. 139, 1903. Philippine Islands.
12. *Stegomyia W-alba*. Theobald, *Ann. Mus. Nat. Hung.* iii. p. 74, 1905. India.
13. *Stegomyia pseudonivea*. Theobald, *idem*, p. 75. Singapore.
14. *Stegomyia simpsonii*. Theobald, *Entomologist*, 38, p. 224, 1905. Transvaal.
15. *Stegomyia powerii*. Theobald, *Journ. Econ. Bio.* i. p. 19, 1905. Natal.
16. *Stegomyia annulisostriis*. Theobald, *Journ. Bomb. Nat. Hist. Soc.* xvi. p. 239, 1905. Ceylon.
17. *Stegomyia mediopunctata*. Theobald, *idem*, p. 240. Ceylon.
18. *Stegomyia* (?) *brevipalpis*. Giles, *Handbk. Gnats*, 2nd ed. p. 384. N.W. Provinces, India.

There are many genera closely allied to *Stegomyia* and at one time included in it, such as *Skusea*, *Macleaya*, *Scutomyia*, etc., but although often abundant species are found they do not call for any special comment. The reader is referred to works on the Culicidæ for full details.

Genus *CULEX* Linnæus.—Formerly all mosquitoes with long male palps and short female palps were included in this genus. A large number have been excluded recently on the grounds of their totally different scale-structure and habits. Separated on scale-structure alone, many of the different genera have been found to have different ova, larvæ, pupæ, and habits (*Stegomyia*, *Scutomyia*, *Mucidus*, *Desvoidea*, etc.). Yet there still remain many species in *Culex* that will have to be excluded on further study.

At present about two hundred and fifty species are placed in *Culex*. Quite half of these must be removed, and the genus retained for those species only that are related to *Culex pipiens* Linnæus, upon which the genus was founded. The characters of true *Culex* are as follows:—

Head clothed with narrow-curved scales above, flat ones at the sides

and with upright-forked scales; the male palpi are long and end acuminate, those of the female are short; the thoracic squamæ are all either narrow-curved scales, or hair-like curved scales, there being no flat scales except on the pleuræ. The fork-cells are moderately long, and the lateral vein-scales are linear. The male genitalia have a leaf-like lateral process. One only has ornamented wings (*Culex mimeticus* Noé) which resembles *Myzomyia* in general appearance. The genus is world-wide. Some are purely sylvan, others entirely domesticated. The sylvan species lay their eggs in pools, streams, crab holes, now and again in tubs and barrels, whilst the domestic forms breed close to and in man's habitations. Not many species of true *Culex* are, however, domesticated. The most important species medically are the following:—

(1) *The Tropical Household Brown Mosquito*—*Culex fatigans* Wiedemann.—Like *Stegomyia fasciata* this gnat has a very wide distribution. It varies very much in size and colour, and in the relative lengths of the fork-cells of the wings. There are several closely related species, but they can easily be distinguished by the shape of the thoracic scales, by the thoracic and abdominal ornamentation, the leg-banding, and the unguis and male genitalia.

The typical *Culex fatigans* has a more or less uniformly scaled thorax, the scales being various shades of golden and golden-brown. Two more or less distinct dark parallel median lines are noticeable on the mesonotum, and the abdomen, which is deep brown and clothed with brown scales, has either creamy or creamy-white basal bands to all the segments and in addition basal white lateral spots. The legs are uniformly brown, the female unguis equal and simple, the fore and mid male unguis unequal, and both uniserrate, whilst the hind are equal and simple. The wings have uniform brown linear lateral scales, the first fork-cell is always longer than the second, its stem variable in length, but never as short as one-fourth the length of the cell.

The females lay their eggs in masses or rafts in rain-water barrels, tubs, tins, cisterns indoors, even in water-jugs and almost any artificial receptacles; they also place them in irrigation canals, fountains, cesspools and wells near houses. As many as two to four hundred eggs are laid in each raft, and they may take from sixteen to twenty-four hours to hatch. The larvæ have a moderately long siphon, and may mature in six or seven days in warm climates. They feed off algæ and water-plants, and frequently come to the surface to breathe. The pupal stage lasts from twenty to fifty hours. Many generations may occur in a year in tropical climates and two or three in subtropical regions.

The distribution of *Culex fatigans* is very similar to that of *Stegomyia fasciata*; the following are recorded localities:—

*Europe*.—South Italy, Portugal, Spain, probably all Southern Europe; the Mediterranean Islands. *Asia*.—Apparently widely distributed. *Africa*.—General. *North America*.—Up to New York State. *South America*.—Brazils, Argentine, Chile, Peru. *West Indies*.—In all the islands. *Australia*.—Abundant along the littoral, spreading inland.

*Most Oceanic Islands.* Roughly, it occurs between 40° on each side of the equator, and to a slight extent just outside this limit. None have been found in Northern Europe or in Canada. In northern latitudes the species is represented by *Culex pipiens* Linn., and *Culex nigripes* Zetterstedt. The means of dispersal are, as in the case of *Stegomyia*, by boats and trains. It was noticed by Skuse that *Culex cibarius* (i.e. *fatigans*) advanced into Australia with the railways. It is well known that it is a passenger on board ship. The pregnant female can remain alive for some months, and so may land hundreds of miles away from its original home and start a colony.

It is *Culex fatigans* that is the main intermediate host of *Filixæ* *tenax*, etc., and it also is the supposed distributor of dengue.

*The Northern Household Brown Culex.*—*Culex pipiens* Linnæus is very closely related, but is usually larger, and can at once be told by the stem of the first fork cell being *very small* and constant in length, never more than one-fifth the length of the cell. The larva has also a much longer siphon than in *C. fatigans*.

*Culex pipiens* is also a household species. It breeds in similar places to the former, but unlike it, it is not always a blood-sucker in all localities. At certain seasons, in certain areas, it is very vicious, in other seasons or other areas it will not bite man at all. It will feed upon other insects, fruit, nectar of shallow flowers. The adult females (unpregnated) hibernate in cellars, outhouses, and any dark corners.

*Culex pipiens* occurs over most of Europe, especially the northern countries, it is found in Egypt, Algeria, Morocco, Madeira, Teneriffe, the northern United States, Canada, and recently it has been found in Cape Colony, doubtless carried in transports during the Boer War, with *Toxotia squithripalpis*.

**Genus TENIORHYNCHUS** Arribalzaga.—The only point of importance now proved about this marked genus, which is frequently mentioned in works on mosquitoes and disease, is that many are vicious biters. The genus is very distinct, being easily separated from the last by the wing-scales being broadly elongated with truncated or semiacute apex, and either of moderate length or very long; the wing-scales are always dense. There are two well marked groups in the genus (1) in which the scales are brown and white or yellow, giving the wings a mottled appearance, and (2) the other in which they are mostly yellow, or rarely brown and large, and the whole insect of large dimensions (*T. auratus*, etc.). The ova of the typical *Teniorhynchus*—*T. fasciculatus*—are deposited in long strips side by side as in *Culex*, and are composed of a large elongated oval area, and a small round apical area. These ribbon-like egg-masses are very characteristic. On the other hand, the yellow group of *Teniorhynchus* lay eggs as seen in *T. fulvus* in long strips, but the ova are placed diagonally side by side, forming rough diamond shaped areas among the egg mass, which may break away from one another (Goeldi). This is another reason for separating them. (Recently Goeldi has formed the genus *Chrysocoonops* for them.)

The siphon in true *Tæniorhynchus* larvæ is similar to *Mansonia*, that is, it is swollen basally, and much contracted apically, and very short. Species occur in South America, Europe (one), and Africa, and several of the yellow group (*aurites* Theobald, *fuscopennatus* Theobald) in Africa, also a closely related yellow form (*fulvus* Wiedemann) in South America, and others (*bresicellulus* Theobald) in Asia, and in Australia (*acer* Walker).

The only other Culicine genus of possible medical importance in connexion with disease is the following:—

Genus *ACARTOMYIA* Theobald.—This genus represented at present by a single species is related to *Grabhamia*, but differs in the head scale-structure. The head is clothed with irregularly disposed flat scales with patches of narrow-curved ones, and numerous upright-forked scales, giving the head a ragged appearance. Otherwise the characters are much as in *Grabhamia*. The larvæ have short thick siphons, and are found in the salt-pans along the shore at Malta, especially in fever areas (Malta Fever). They are very vicious biters.

The single species is *Acartomyia zammittii* Theobald, and so far has been found only in Malta (vide *Mono. Culic.* iii. p. 201, 1903).

#### HEPTAPHLEBOMYINÆ

The general notion amongst medical men is that a true mosquito can be recognised by its six-veined wings. This, however, is not an absolutely reliable guide, because three species are at present described in which a definite seventh-scaled vein occurs. Otherwise, the species much resemble *Culex*. They bite viciously in Madagascar, where three species occur (*Heptaphlebomyia argenteopunctata*, and *H. monforti* Ventrillon, and another). One species is also abundant in West Africa (*H. simplex* Theobald).

#### AEDINÆ

Amongst the thirteen genera of Aedinæ only one need be mentioned, namely, *Uranotænia*. A few of the others are very vicious biters as far as we know at present. The genus *Deinocerites* Theobald is limited to the West Indies; the larvæ live in crab-holes, and the adults are peculiar in that the second segment of the antennæ is very long.

Genus *URANOTÆNIA* Arribáizaga. These are all very small mosquitoes, about 2 mm. long. The head is clothed with flat scales and so is the scutellum, but the easiest diagnostic feature is the extremely small first fork-cell.

Some seventeen species are known, of which eight occur in South America and the West Indies, three in the East Indies and Malay, four in Africa, and one in Australia.

The adults bite during the day in grassy places and near where they breed; none are known to be domesticated. The larvæ occur in pools and small water-holes, and have very short siphons, coming thus between

the Anophelinæ and the Culicinæ; they lie to some extent in Anopheline fashion at the surface, but somewhat obliquely. Some are coloured red, blue, and green (*U. geometrica* Lutz, etc.), others black (*U. lowii* Theobald) or opaque creamy white (*U. pulcherrima* Arribáizaga). The adults have frequently beautiful coloured scales on the thorax and abdomen, and usually a brilliant line of scales on the base of the wing. Possibly some marsh fevers may be traced to them, as several are very vicious and persistent biters.

Amongst the *Metanototrichæ* there are no forms of especial medical interest, as far as is known at present.

The section is separated by the character of the metanotum, which in all other Culicidæ is nude, whilst in this section it has either scales (usually flat ones) or distinct chætæ upon it (Fig. 97, *A* and *B*). This at once separates them from the other mosquitoes. In some this extra scaly nature gives a brilliant coloration, and even the chætæ give the gnat a very distinct appearance. There are two groups of them, according to Lutz's classification, (*a*) the Hyloconopinæ, in which the males have

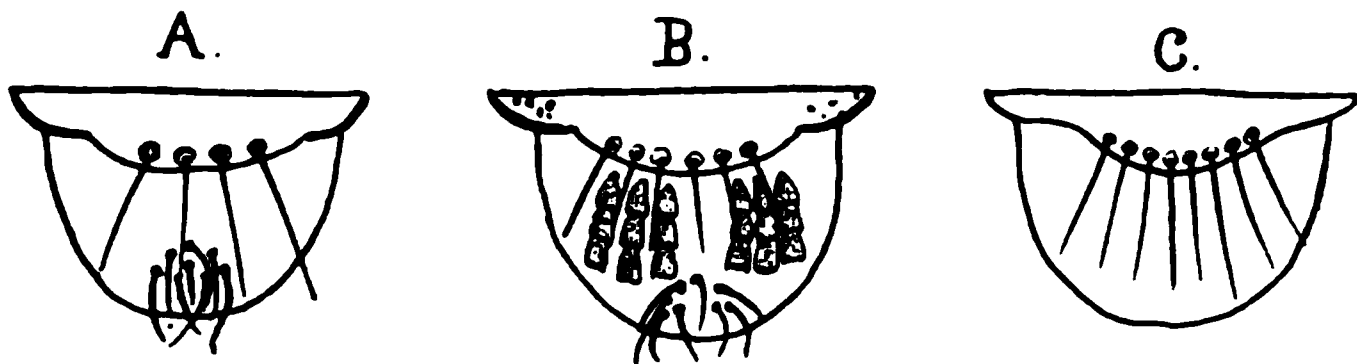


FIG. 97.—Scutella and Metanota of *A* and *B*, *Metanototrichæ*; *C*, of *Metanotopsila*.

long palpi and the female short, and (*b*) the Dendromyinae, in which the palpi are short in both sexes.

All known species and genera of the former group occur in the West Indies and in South America. They are usually brilliantly coloured, and are all sylvan in habits.

The Dendromyinae contain one very quaint genus—*Sabethes* Desvoidy, in which the tarsi of one or more pairs of the legs have the scales greatly elongated, forming distinct paddle-like areas. The males and females are exactly alike except for genitalia and ungues. These large quaint *Sabethes*, are wood-mosquitoes, but they invade tents and native huts, and bite quite viciously.

The other genera—*Wyeomyia* Theobald, *Phoniomyia* Theobald, *Dendromyia* Theobald—are small sylvan mosquitoes, which are often very annoying to travellers in the South American forests. The last genus is found in North America (*D. smithii* Coquillett), the first in the West Indies (*W. grayii* Theobald, and *W. pertinans* Williston), and in Ceylon (*W. greenii* Theobald). They occur in hill woods and forests, and bite very viciously; now and then they come near habitations. When at rest they throw their hind legs right forward over their head.

The larvæ of *D. smithii* Coquillett, live and pass the winter in pitcher-plants. They are not affected by repeated freezing and thawing.



The eggs are laid on leaves singly or in small groups, fastened to the side or floating on the surface. In the late season the adults lay their eggs on new leaves, even if they are dry.

The genus *Phoniomyia* occurs in South America and West Indies (*P. longirostris* Theobald) and in New Guinea (*P. bimaculipes* Theobald) and in India (*P. idica* Theobald). It can at once be separated from the *Wyeomyias* by the very long proboscis.

The *Dendromyias* occur in South America and West Indies; they differ from the *Wyeomyias* in having the wing-scales large and broad instead of linear.

Many of these so-called wood-mosquitoes breed in bromelias in Brazil, and are a great nuisance in the forests and swamps.

The genus *LIMATUS* Theobald is very peculiar, in that the proboscis is sharply elbowed. One species only occurs which bites viciously in South America. The larvæ figured by Goeldi have a short siphon, gradually swelling basally.

The "Phantom Larvæ" Gnats (*Corethrinæ*) do not bite, and although previously included in the *Culicidæ* they are best separated, as they have no long piercing proboscis.

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F. V. T.

BLOOD-SUCKING AND OTHER FLIES KNOWN OR LIKELY  
TO BE CONCERNED IN THE SPREAD OF DISEASE

By ERNEST E. AISTEN, F.Z.S.

THE creatures with which we are concerned in this article are members of the Order **Diptera**, or two-winged flies, which may briefly be defined as insects with but one pair of wings, a thorax coalesced into a single mass, and mouth-parts adapted for piercing and sucking, or for suction alone. The preliminary stages (larva and pupa) are in outward form together dissimilar to the adults, and, as in all other insects, the *period of growth* is confined to the larval stage. The latter fact is worthy of note, since many people appear to be under the impression that flies *grow*, and to believe, when they see a fly apparently belonging to a species with which they are acquainted, but of subnormal size, that it is a young specimen. It cannot, therefore, be insisted upon too strongly that a fly on emerging from its pupa-case has attained its full dimensions, and that, thenceforth, apart from the expansion of the tissues that takes place shortly after leaving the puparium, and a possible subsequent distention of the abdomen due to the ingestion of food (as in many blood-sucking flies), or the development of ova in the females, any increase of bulk is out of the question. Consequently, on meeting with what appears to be a diminutive specimen of a known species, it is safe to conclude, either that the smallness of size is due to local or individual variation, in the latter case usually the result of a shortage of food in the larval state, or else that the insect belongs to a distinct species.

Flies that are already known to be disseminators of disease, or that may sooner or later prove to be so, are either blood-sucking forms, or species which, while incapable of sucking blood, may sometimes act as mechanical living vehicles of infective matter. The species falling within the latter category will be dealt with shortly in the concluding portion of this article: our immediate concern is with the blood-sucking forms.

## Blood-Sucking Flies

Among Diptera as a whole the habit of feeding upon the blood of warm-blooded animals is highly exceptional, although in two families (Culicidae and Tabanidae) it is universal in the female sex, with the possible exception of certain species of *Limnoria*. Apart from the Gnats or Mosquitoes (Culicidae) [vide Article, p. 122], with which we are not here concerned, blood-sucking species of flies occur, so far as is known at present, only in the following families — Chironomidae (midges), Simuliidae



(sand-flies), Psychodidæ, Tabanidæ (horse-flies, serut-flies, etc.), Leptidæ, Muscidæ (tsetse-flies, etc.), and Hippoboscidæ.<sup>1</sup> For the special purposes of this work it is unnecessary to consider any flies but those that regularly suck human blood as often as they have the opportunity, or in which the blood-sucking habit, as affecting human beings, is sufficiently marked to have attracted the attention of observers. Consequently we may safely ignore the Hippoboscidæ, which are normally parasitic upon mammals and birds, and only occasionally stray on to human beings. The reddish-brown, horny flies of the genus *Hippobosca* are parasites of horses, donkeys, camels, cattle, and dogs, and few if any instances have yet been recorded of their having bitten man; but in passing it may be worthy of note that in the Transvaal Dr. Theiler has succeeded experimentally in inoculating cattle with *Trypanosoma theileri* by means of the common South African *Hippobosca rufipes* von Olfers.

In all blood-sucking flies the organs, by means of which the act of sucking blood is effected, consist of a proboscis, attached to the under side of the head, with which the wound is inflicted, and a muscular pharynx contained within the head, by means of which the blood is pumped into the insect's alimentary canal. In the blood-sucking Muscidæ (tsetse-flies and their allies) the proboscis itself, which in these forms is stiff and chitinous, and armed with a remarkable series of teeth at its extremity, is generally regarded as the piercing organ. In the case of all the other families enumerated above, however, the actual proboscis or labium is soft and fleshy, and merely serves as a sheath to contain the piercing chitinous lancets. The full complement of the latter, as seen in a female horse-fly, sand-fly, or midge, and taken in order from above, is as follows:—an unpaired chitinous plate, termed the labrum, or labrum-epipharynx, which closes in the basal portion of the tube formed by the labium, the distal portion of the tube being constituted by the labium itself; a pair of broad lancets, or mandibles, armed with a minutely serrated cutting edge; a pair of more slender lancets, or maxillæ; and lastly, the hypopharynx, a median unpaired tube, the terminal portion of the fused ducts of the two salivary glands, whose outlet is at its extremity. In the blood-sucking Muscidæ the mandibles and maxillæ are absent, so that in addition to the proboscis, or labium, we find only the labrum and hypopharynx. In the phlebotomic Muscidæ both male and females suck blood, and the mouth-parts in both sexes are alike; but in the case of all the other families with which we are here concerned the blood-sucking habit is confined to the female sex, and the mouth-parts in the males are much reduced. In all forms a pair of maxillary palpi is attached to the base of the proboscis, and these structures, soft and much swollen in many horse-flies, are in the tsetse-flies firm and rigid.

<sup>1</sup> The Blepharoceridæ, though usually included among the families of Diptera containing blood-sucking species, are here omitted, since no member of this family has actually been observed to suck blood. In the case of the supposed phlebotomic form, the Brazilian *Curupira* (*Paltostoma*) *torrentium* F. Müll., suspicion at present simply rests upon Friessmüller's statement that a certain number of the females possess mouth-parts of the blood-sucking type.

forming a protecting sheath to the proboscis, to which in life they are applied so closely as to conceal it.

In the act of sucking blood, the secretion of the salivary or poison glands is discharged into the wound from the orifice at the tip of the hypopharynx, and the function of the secretion would appear to be to keep the blood fluid and to stimulate its flow. From the pharynx of the fly the blood passes into a large, thin-walled crop, situated in the anterior part of the abdomen, whence it is regurgitated by slow degrees, through a valvular organ, known as the proventriculus, into the mid gut, where it is gradually digested. The remarkable discovery, published in 1904 that an African Muscid, which itself is incapable of sucking blood, has an active blood-sucking larva will be referred to in greater detail on p. 184.

Before proceeding to give a brief account of blood sucking flies, grouped under the different families, such as, with the help of the figures, will, it is hoped, enable the reader to form a correct idea of the affinities and probable life history of any species with which he may come into contact, it seems advisable to devote a few moments to the consideration of the present state of our knowledge concerning the relation between these insects and disease in man. At the outset, then, it must be confessed that definite knowledge is as yet very limited, and that, apart from mosquitoes, the only blood-sucking flies that have been proved to disseminate disease in man under natural conditions are the tsetse flies of the species known as *Glossina palpalis*, which has been shewn by the researches of Colonel Bruce and others to convey the trypanosome of sleeping sickness in Uganda. The evidence, such as it is, tending to shew that any biting-fly may occasionally convey the bacillus of such a disease as malignant pustule from an infected animal to man has, with much other matter bearing upon the relation between insects and ticks and disease in human beings, been well summarised in Dr. Nuttall's valuable memoir published in 1899 (1). But the accidental direct transference of *Bacillus anthracis* or any other pathogenetic organism is very different from what takes place in the case of malarial fever, yellow fever, or sleeping sickness, where certain species of Diptera have become the hosts and disseminators of certain species of parasites. Anything beyond this, however, is, so far as our present knowledge goes, merely a possibility, though in estimating possibilities we cannot fail to be influenced by recent discoveries relating to parasitic diseases of domestic animals, which, in the case of trypanosomiasis at any rate, are caused by haematozoa congeneric with *Trypanosoma gambiense*—the parasite of "trypanosoma fever" and sleeping sickness. Thus, in November 1905, it was stated by Lieut. Colonel Maudslayi, R.A.M.C., that in Mauritius surra in horses, mules, and cattle, which is caused by *Trypanosoma evansi*, is "almost certainly" disseminated by a species of *Stomoxys* (2). Surra is stated to have been "introduced into Mauritius from India in 1902-3", in the brief space of time that has since elapsed it has ravaged the island, and is apparently conveyed by the bite of a local blood-

sucking fly of the genus mentioned. This, at least, points to the possibility that some species of *Stomoxys* may be a disease-carrier in the case of man; though it must be noted that in Uganda recent attempts by Captain Greig, I.M.S., and Lieutenant Gray, R.A.M.C., to infect monkeys with the parasite of "nagana" (tsetse-fly disease of animals), and with another species of *Trypanosoma*, by means of a species of *Stomoxys* common in Uganda proved negative (3), as did previous experiments by other members of the Sleeping Sickness Commission with the parasite of sleeping sickness and the same fly. It is believed by Dr. Émile Brumpt, who is entitled to speak with some authority upon the subject, that *Trypanosoma brucei*, the parasite of nagana, which in Zululand and other parts of Africa is disseminated by *Glossina morsitans* and *Glossina pallidipes*, is carried in addition by at least three other species of tsetse-flies; and in Uganda, Greig and Gray (3) have proved that this parasite, as also a third species of trypanosome, can be conveyed by *Gl. palpalis*, the disseminator of sleeping sickness. In 1904 Brumpt's studies led him to believe that sleeping sickness may also be transmitted by several species of *Glossina* (4). Should this supposition, which is shared by Greig and Gray, prove to be well founded, it would obviously be dangerous to allow cases of sleeping sickness to be introduced into any part of Africa previously free from the disease, but infested by any species of tsetse-fly.

Returning for a moment to *Stomoxys*, we may note that Noë has shewn that *Filaria labiato-papillosa*, of the ox, develops in the muscles of the head of the common European *Stomoxys calcitrans*, and is transmitted by the fly (5). Both in the case of *Stomoxys* and in that of blood-sucking flies other than Muscidae, it is highly desirable that an exhaustive series of experiments should be undertaken in all parts of the world, for the purpose of determining whether any species acts as the carrier of disease from man to man *under natural conditions*, and not merely when the proboscis of the fly is used experimentally as an "inoculating needle."

Turning now to the flies themselves, and taking the families mentioned above in systematic order, we commence with the **Chironomidae** or **Midges**. Midges abound in most parts of the globe, but the blood-sucking species are confined to the genus *Ceratopogon*, and a few small genera closely allied thereto. Even in *Ceratopogon*, which is universally distributed, and at present includes more than a hundred described species, the blood-sucking habit is exceptional. Although exceedingly minute, for the females are seldom more than  $1\frac{1}{2}$  or 2 mm. in length, midges are among the most irritating and blood-thirsty of insects, and, since the individuals of the blood-sucking species usually occur in swarms, they frequently constitute a veritable plague. Their very smallness renders them additionally formidable, since it enables them to pass through the meshes of an ordinary mosquito net. In general appearance many tropical species of midges are very similar to the common European *Ceratopogon pulicaris* Linn. (Fig. 98), which is often a pest in many parts of the British Islands in early summer. Although the body is naturally dusky in colour, the abdomen in female midges often appears rosy when

distended with blood. The legs are sometimes banded, and the wings, which in the resting position are carried flat, closed one over the other like the blades of a pair of scissors, are hairy in many species, and frequently mottled with brown. The larvæ of the naked-winged species are usually aquatic, and live among algæ on the surface of stagnant water; they are whitish worm-like creatures, with long narrow heads. In the case of the hairy-winged species, the larvæ are generally terrestrial, and are found in decaying vegetable matter or in the flowing sap of trees.

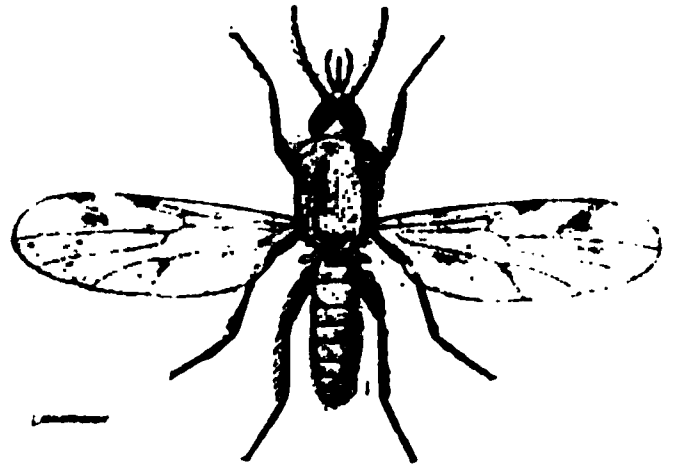


FIG. 98.—*Ceratopogon pulicaris* Linnaeus.  
♀ × 10. Great Britain.

The midge known as the *miruim* in the neighbourhood of Pará, Brazil, which has recently been described by Dr. E. A. Goeldi (6) under the name *Hæmatomyidium paraense*, is a true *Ceratopogon*, perhaps identical with *C. phlebotomus* Will., of St. Vincent, W.I. According to Dr. Goeldi, the *miruim*, the female of which is rather less than 2 mm. in length, invades houses, and is a most troublesome blood-sucker; its bite is painful, and a fairly large circular inflamed zone always develops round the punctured spot. The species is diurnal, and bites at any hour, though usually most abundant at the time of low tide; from the latter fact it would appear probable that the *miruim* breeds on the shores of the Pará River, perhaps in the pools of brackish water left exposed when the tide goes down. Of another species of *Ceratopogon*, common in many parts of Uganda, Dr. Christy writes that it "bites terribly, leaving an irritating wheal, which itches for days. It makes a sharp, short, peevish buzz when settling, fully as loud as a mosquito. It attacks the wrists chiefly, but is able to pass beneath a sheet, and bite the ankles and feet. Many were frequently found full of blood on turning down the bedclothes. I have met with a similar fly, with the same habits, at Ahmednuggar (Bombay Presidency), India" (7).

The blood-sucking midge known in Cuba as the *jejen* was described by Poey in 1853 under the name *Oecacta furens*. It does not exceed 2 mm. in length, and is brownish-black in colour, with reddish antennæ, white legs banded with brown, and mottled wings. In Cuba, where it is chiefly confined to wooded and shady spots at the mouths of rivers and in the vicinity of the sea, the *jejen* is said to be a scourge of man and animals, its small size enabling it to enter the eyes and nostrils. According to Ellis (8), the species has also been found in Jamaica, during the month of November, in numbers on the sea-beach of the Palisadoes, "a sandy strip of land separating Kingston harbour from the Caribbean Sea."

**Simuliidæ.**—(In India called "*Pipsa*" or "*Potû*" flies; "*Brûlots*" of the French Canadian trappers in British Columbia; in the United States known as black flies, buffalo-gnats, and turkey-gnats.) This family consists of the single genus *Simulium*, comprising at present some seventy

described species, a certain number of which, however, are doubtless synonyms. The species are extremely difficult to distinguish one from another, so much so that even the number of British species is as yet completely uncertain; in general appearance there is usually a bewildering similarity, coupled with a marked deficiency of good structural characters. This is especially true of the females, which, being the blood-suckers, are most commonly captured; moreover, characters derived from the females alone are insufficient for the distinction of species in this genus, in which there is considerable sexual dimorphism, as well as a marked difference in habits between the sexes. The genus *Simulium* is universally distributed, and besides being abundant in the tropics the flies occur in myriads in the temperate and colder regions of the earth, even so far south as Tierra del Fuego. The females are excessively greedy of blood, and, besides persecuting human beings, those of certain species are greatly dreaded for their attacks on stock. In appearance they are small black or greyish flies, sometimes orange-coloured or with a yellowish base to the abdomen, varying in length from  $1\frac{1}{2}$  to 4 mm. according to the species, with a humped thorax, short, straight antennæ, delicate iridescent wings, stout legs, and a short and inconspicuous, albeit exceedingly serviceable, proboscis. The males are usually darker than the females, and frequently exhibit silvery markings upon the thorax.

The preliminary stages are passed in running water, close to the edge of which the eggs are deposited on stones or plants in a compact layer or gelatinous mass. The larva, which in shape somewhat resembles a tiny contracted leech, though capable of crawling in a looping fashion, is usually to be found in a more or less erect position attached by a posterior sucker to the stem of a water-plant, stone, or other object beneath the surface. When full-grown the larva spins a silken cocoon, within which the change to the pupal state is effected, and in which the pupa remains motionless, until, after the lapse of about a week in temperate climates, though in the tropics a shorter period possibly suffices, the back of the thorax splits to permit the escape of the perfect insect, which ascends to the surface in a bubble of air. The male flies, which are incapable of sucking blood, frequently swarm and dance at some height above the ground.

Although no attempt has yet been made to suggest that the species of this genus are disease-carriers, they would at least appear to be eminently qualified to act as such by reason of their pertinacity as blood-suckers and almost incredible abundance in certain localities; while at any rate their attacks frequently have an injurious effect upon native populations, as well as upon explorers and others who have occasion to penetrate into their haunts. Thus, with reference to *Simulium damnosum* Theobald, a species locally known to the natives as *mbwa*, a correspondent in Uganda recently stated that "Its bite is very poisonous and irritable, causing large swellings which usually end in sores. Localities where this fly is present are very sparsely inhabited." Writing of this species

so with reference to Uganda, Dr. Christy (9) says that it occurs in a belt "about twelve or fifteen miles in length, by three or four miles in width on the right bank of the Nile. "In this area the flies swarm at certain seasons in millions," and become such a pest that the natives are forced to leave their plantations. Dr. Christy further states that "the bite of this small fly is a very severe one, and causes a wheal which itches intolerably, and is marked by a large drop of blood." Several species of *Simulium* are found in India, where, under various vernacular names, they are well-known pests. The female of *Simulium indicum* Becher (Fig. 99), found in Assam, is 3 mm. in length, and deep black, except the base of the abdomen, which is yellow; the femora, except the tips, are more or less yellowish, the tibiae white on the basal half, and the costal margin of the wing is rather stout. Of this species Major Hall, I.M.S., writes that it "infests the foot-hills of the Himalayas in North Lakhimpur, Assam, where the flies are locally known as 'Dam Dims'; they have a very poisonous bite, and interfere a good deal with



FIG. 99.—*Simulium indicum* Becher. ♀ × 10.  
Annam.

be tea-coolies. They come out in January, and continue until March and April." Farther to the west along the Himalayas the local species of *Simulium*, in some cases certainly distinct from *S. indicum*, are known by other vernacular names such as "*Potú*," or in Sikkim as "*Pypsa*," designations that are doubtless applied indiscriminately to more than one species. Specimens of *Simulium* recently received from the Kangra valley belong to two different species, both distinct from *S. indicum*. The late Mr. Lionel de Nicéville gives the following observations on "*Potú*," from information supplied by Mr. Vincent A. Mackinnon (10):—At Mussooree it is very plentiful in the spring, but small numbers can be found at all seasons. In the western Himalayas it occurs at Mussooree, Chakrata, and thence northwards, as far as the Niti Valley, near the snows. The Balti people say that it is well known in their country (Kulistan). It is found both in forests and in open grass-covered downs, and at all elevations, from 3000 to 10,000 feet. At the latter elevation Mr. Mackinnon was once so badly bitten that he had to lie up from the effects for two days. The effects of the bite vary greatly in different people: to some it causes but little apparent inconvenience, a small black spot only being visible where the insect has bitten; in other people it



causes intense irritation, which, when the itching places are scratched, gives rise to large lumps beneath the skin; these may be some days before they disappear. . . . When the Chakrata-Saharanpur road was being constructed, numbers of the workpeople were reported as having died from the effects of the bites. In the western Himalayas the fly is called *Potû* in Hindustani, *Phisniuri* in Pehari, and *Phisho* in Balti." According to Mr. E. C. Cotes, who collected notes on the *Potû* from forest officers in the north-west Himalayas (11), "in the North-West Provinces it is said sometimes to occur in such numbers that the air seems to be full of the flies, but it is less abundant in Sikkim, where the climate is moister. The worst months are April, May, and June, *i.e.* the hot season, but the flies are not uncommon in the low valleys in February and March. When the rainy season sets in they usually disappear, and are not seen again until the following spring. The insect flies noiselessly, and its bite in the first instance is so painless that the creature is seldom noticed at work until its yellow and black body is to some extent coloured with the blood it has absorbed. It is then too late to do much good by brushing it away. It leaves a characteristic mark due to the presence of a little globule of blood, about the size of a pin's head, beneath the skin. The bite soon becomes irritable, but the effects vary in different individuals. Generally speaking, the irritation passes off in a few days, but in the case of newcomers and persons in bad health it often causes troublesome sores and ulcers. . . . The common method of treatment is to squeeze the blood out of the wound immediately, as this allays the intolerable itching, though even then some swelling is usually produced. Deodar and eucalyptus oil also are freely used for rubbing over the hands and face to keep off the insects, which are most annoying where they occur." The species known and feared in certain parts of the Amazon district, Brazil, and especially on the Rio Purús, under the name "*pitum*," has recently been described by Dr. Goeldi (12) as *Simulium amazonicum*. There is reason to believe, however, that it is identical with the North American *S. venustum* Say (*pertinax* Kollar). The well-known and dreaded "Borrachudo" of Southern Brazil also belongs to the genus *Simulium*, and the name is perhaps applied to more than one species.

Details of remedies recommended for lessening the pain of the bite of *Simulium* and preventing inflammation have been given by Brauer (13) who says that all plans to diminish the number of these insects hitherto have been unsuccessful, since the larvæ cannot be attacked, or only to a limited extent. The same writer adds that smoke, "produced by putting live coals into heaps of dung, leaves, hay," etc., is a protection against the flies, as is also "an embrocation of tobacco decoction, or kerosene oil."

**Psychodidæ**, genus *Phlebotomus* (called *sand-flies* in the Sudan and Ceylon).—Although it has hitherto been believed that the blood-sucking species of this family are confined to the genus *Phlebotomus*, there is some reason to think that one or two species of the genus *Sycorax*, one of which occurs in Algeria, also suck blood, though it is not known whether they

attack human beings. The small, midge-like, yellowish-brown hairy flies of the genus *Phlebotomus* (Fig. 100) need not detain us long, for they have not yet been studied systematically, and practically nothing is known as to the habits of the three or four species that occur in the south of Europe, the Mediterranean sub-region, the Anglo-Egyptian Sudan, Uganda, and Ceylon. As in the case of the harmless species of this family, the body and wings are densely clothed with long hair, but *Phlebotomus* may be recognised by the slender shape of the body, which measures from  $1\frac{1}{3}$  to 2 mm. in length, long legs, and by the prominent proboscis, which projects vertically beneath the head. The life-history is practically unknown, but the preliminary stages are passed in water, or in cesspools or other liquid filth.



FIG. 100.—*Phlebotomus* sp ♀ × 10.  
Ceylon.

**Tabanidæ** (*horse-flies*, or *breeze-flies*; sometimes called *gad-flies*; *scrut-flies* on the Upper Nile; *mangrove-flies* in West Africa—a name, however, that also includes tsetse-flies).—This is a family of blood-suckers, for, as already stated, the habit, as in *Simulium*, is universal in the female sex, with the possible exception of certain species of *Pangoniu*. The Tabanidæ, besides being world-wide in distribution, are also one of the largest of all the families of Diptera, the number of described species being now little short of 1600, although this total is certain to be somewhat reduced when a much-needed revision is undertaken. More than half of the species (over 900) belong to the genus *Tabanus* (Fig. 105), though the other principal genera, *Hæmatopota* (Fig. 104), *Pangonia* (Fig. 102), and *Chrysops* (Fig. 101), are also rich in species. In appearance the Tabanidæ, some of which are among the largest of Diptera, are bulky-bodied flies, ranging in length from about 6 mm. in the case of a small species of *Chrysops*, to more than an inch in that of the largest species of *Tabanus*. The head is large, convex in front, and in the male almost wholly composed of the eyes, which meet together above in that sex, but are separate in the female. The eyes in life are extremely beautiful, being usually of a greenish colour, generally marked with transverse stripes, wavy bands, or spots of purplish-brown; the eyes in *Chrysops*, in which the ground-colour is a brilliant metallic gold or purple, are especially remarkable. The pattern of the markings varies with the species, and is consequently of value for specific distinction; but unfortunately in dried specimens the eyes fade into a dull brown, and the markings as a rule disappear entirely, though they can usually be restored temporarily by damping the specimen. The antennæ, which are always prominent, are especially long and slender in the genus *Chrysops* (see Fig. 101), in which they serve as a distinctive character. The proboscis in most genera is short and stout, and protrudes vertically



beneath the head, the piercing stilets being enclosed in a fleshy lobe in *Pangonia*, however, it is stiff and slender, generally more or less zontal, and usually considerably elongated. In the case of certain species such as *Pangonia longirostris* Hardw., which is found in the Hima



FIG. 101.—*Chrysops dipter* Fabricius. ♀ × 4.  
India and Ceylon to Hong-Kong.

and in which the proboscis is many times longer than the body, possible that the insects are not blood-suckers but feed on other food, as recently pointed out by Lutz (14), should the proboscis very long, the enclosed piercing stilets do not reach the tip by a



FIG. 102.—*Pangonia beckeri* Bezzi. ♀ × 2.  
Somaliland.

way. In species of *Pangonia* with a very much elongated proboscis, individual differences in the length of the labium are often noticed, as are stated by Lutz to be due to the fact that "in true species *Pangonia* the labium is protrusible and retractile, its basal portion

le of being rolled up spirally inside the posterior part of the buccal 7." In *Pangonia beckeri* Bezzi, a Somaliland species illustrated in 102, the proboscis is relatively short.

a coloration the majority of Tabanidæ are somewhat sombre, the iling hue being generally some shade of brown, though the abdomen



FIG. 103.—*Lepidowaga lepidota* Wiedemann. ♀ × 4.  
Mexico to Brazil.

ten lighter, or prettily adorned with lighter markings, which, being to a coating of short hair, are easily rubbed off. In the case of *lepidowaga lepidota* Wied. (Fig. 103), called by Bates "the scourge of the r Amazons," and known to the local Indians as the "*motuca*," the



FIG. 104.—*Hæmatopota pulchrithorax* Austen. ♀ × 4.  
Anglo-Egyptian Sudan to South Africa.

black body is covered with a coat of minute greenish iridescent like hairs. In many species, as in all those of the genus *Chrysops* 101) and some species of *Tabanus* (Fig. 105), the wings are conspicuously banded with blackish-brown, while in *Hæmatopota* (Fig. 104) shew an intricate pattern of light markings on a dark ground.

The eggs of Tabanidæ are deposited in masses (in one flat tier in the case of *Chrysops* and probably in that of *Pangonia* also, but in a sub-conical

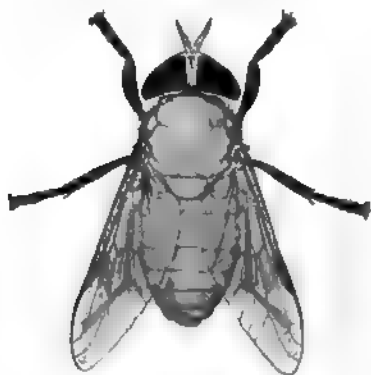


FIG. 103.—*Tabanus fasciatus* Fabricius. ♀ × 2.  
West Africa.

pile of several layers in that of *Tabanus*) on rushes or other smooth surfaces over water or wet ground (15). The larvæ, which in the majority of cases live in the wet sand, mud, or vegetable débris at the margins of rivers, while others are found in earth or water, are glassy, whitish, cylindrical grubs, tapering at each extremity, with a retractile chitinous head. The first seven abdominal segments (i.e. all except the last) are each provided with a circlet of retractile fleshy protuberances, which assist in locomotion.

Tabanid larvæ are carnivorous, and burrow actively in search of food, which consists of beetle-larvæ, snails, worms, etc. The pupæ, which resemble those of Lepidoptera, but are distinguished by the presence of a pair of large ear-shaped spiracles on the dorsum of the thorax, are generally found concealed in damp rubbish at the edge of water.

Female Tabanidæ are among the most persistent of blood-sucking flies, although certain species appear to attack man only exceptionally. The quietness with which the species of *Hæmatopota* and *Chrysops* and the smaller species of *Tabanus* alight on their victims is remarkable, the sharp prick of the bite being often the first intimation of the presence of the fly. The species of *Pangonia*, however, and the larger species of *Tabanus* betray their approach by their loud hum. Tabanidæ are creatures of the open country, woods, roads frequented by horses and cattle, and river-beds; they seldom enter houses, and should they do so they appear to recognise that they are out of their element, and shew no disposition to bite. The biting powers of Tabanidæ are well known to all who have had practical experience of them: a correspondent writing with reference to species met with in swampy localities near Gambaga, West Africa, states that "they bite with ease through two thicknesses of clothing, such as a pair of breeches with drawers underneath." The *motuca* (Fig. 103), already alluded to, is found in Central America as well as in Equatorial Brazil. With reference to the swarms of this fly encountered near Serpa on the Lower Amazons, Bates writes that "its puncture does not produce much pain, but it makes such a large gash in the flesh that the blood trickles forth in little streams. Many scores of them were flying about the canoe all day, and sometimes eight or ten would settle on one's ankles at the same time. It is sluggish in its motions, and may be easily killed with the fingers when it settles" (16).

Many African species of *Tabanus* have a very wide range: thus

*Tabanus africanus* Gray, a handsome species with yellow body, black legs, and the basal two-thirds of the wings prettily banded with brown, is found from Anglo-Egyptian Sudan to Natal, and also occurs in the East Africa Protectorate. Similarly *Tabanus serratus* Lw., one of the species found in Uganda, is very widely distributed upon São Thome I., in the Gulf of Guinea, where it is said to persecute human beings, especially natives, with peculiar pertinacity (17).

Under the name "*serut flies*" several species of *Tabanus* are well known to British officers attached to the Egyptian Army as a scourge of the Upper Nile. One of the commonest of these, in the vicinity of Kodok (Fashoda) at any rate, is *Tabanus sorvus* Walk., a reddish-brown species varying from rather less to rather more than half an inch in length, with longitudinally striped abdomen and clear wings. Serut-flies do not seem to be found continuously along the banks of the river, but appear to be confined to certain tracts recalling the "belts" well known in the case of the tsetse-flies. In a letter dated "Wau, Bahr el Ghazal, Sudan, December 6, 1903," the late Captain H. E. Haymes, R.A.M.C. (attached E.A.), wrote as follows: "The first serut met with going south is at Goussou-Gooma. At Fashoda they are more numerous, and as the papyrus and sedge commence they disappear, i.e. 200 miles south of Fashoda. They appear again, but in small numbers, at Kirro, a Belgian post, and continue to Kefuf, also a Belgian post. Then they disappear again for 100 miles, and appear again at Dufie, from which post they extend 100 miles south."

In view of the successful results that of late years have in some cases attended the efforts of economic entomologists to reduce the numbers of certain insect pests by cultivating their natural enemies, it may perhaps be worthy of note that in the adult state Tabanidæ are often preyed upon by robber flies (*Asilidæ*), and by sand wasps of the family *Bembecidæ*, while their eggs are sometimes infested and destroyed by parasitic Hymenoptera.

**Leptidæ.**—The members of this family are slenderly built flies of moderate size (6 mm. to 13 mm. in length), usually with a short proboscis, and with the wings, in which the arrangement of the veins resembles that seen in the Tabanidæ, often blotched with brown. Some shade of brown or yellowish brown generally forms the prevailing colour of the body, and the abdomen usually tapers towards the tip. The preliminary stages, so far as known, are passed in vegetable mould or rotten wood. The species of the sub-family *Leptinæ*, including the genera *Lepta* and *Symphoromyia*, have a short and noiseless flight, and are fond of resting motionless and head downwards upon the trunks of trees in shady places. Leptidæ have rarely been known to molest man, and their relation among blood sucking forms at present rests upon a few isolated observations. In France two common European species of *Lepta* have been observed to suck human blood, while the same habit has been noticed in California and Arizona in the case of a species of *Symphoromyia*. According to Philippi, *Trichopalpus obscurus* Phil., a species with an elongated proboscis, common in the Province of Valdivia, Chile, in December and January, is a greedy blood sucker.

**Muscidae** (tsetse-flies and their allies).—The blood-sucking species of Muscidae are few in number, but, apart from the mosquitoes, they are by far the most important of all phlebotomic Diptera, since they include the tsetse-flies (genus *Glossina*), one species of which is now so well known as the disseminator of sleeping sickness, while others convey "nagana" or tsetse-fly disease, which is equally fatal among domestic animals. With the exception of those belonging to *Stomoxys*, the species of other genera which feed on blood seldom molest human beings, and are of more importance to the stock-raiser and the veterinary surgeon than to the medical man. The possible importance of *Stomoxys* to the student of tropical diseases has already been hinted at, and little more need be said with regard to this genus, which, perhaps with the exception of South America, is universally distributed. Not more than a dozen species are at present known, but it is probable that some of these are not really distinct, while a few others have yet to be described. The species are all very similar in appearance, and, like the tsetse-flies themselves, are lacking in structural characters for their distinction. Though somewhat more stoutly built, in size and coloration they present such a resemblance to their near relation the house-fly (*Musca domestica* L.) as to deceive the un-



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FIG. 106.—*Stomoxys calcitrans* Linnaeus. ♀ × 5.  
(In resting position.)  
Europe, India, United States.

initiated, though the little black piercing proboscis, which in life may always be seen projecting horizontally in front of the head, affords an infallible means of recognition. The grey or olive brown body generally exhibits a lighter median stripe on the thorax and dark spots or transverse bands on the abdomen. The larva is a white maggot, closely resembling that of the house-fly, and is found in horse-droppings and manure heaps. The perfect insect infest stables and cow-sheds, and are generally to be found in the vicinity of horses and cattle. In the resting position the wings project at an angle from the body, as shewn in Fig. 106. The common European *Stomoxys calcitrans* L. (Fig. 106) is very widely distributed, for it abounds in the United States, while specimens from Northern India are indistinguishable from British examples.

The tsetse-flies (genus *Glossina* Wiedemann) are confined to Africa where, however, as shewn in my recent map (18), they have a very wide distribution in the tropical and (in S. Africa) sub tropical zones. Roughly speaking, so far as our present knowledge goes, the northern boundary of the genus may be represented by a line drawn from Cape Verde

across the middle of Lake Chad to the Nile just south of the twelfth parallel of north latitude and thence to the east coast at  $4^{\circ}$  N.; while its southern limit may be similarly shewn by tracing a line from the mouth of the Cunene River, the southern boundary of Angola, to the north-east extremity of St. Lucia Lake, in Zululand. Within this area tsetse-flies are not found continuously, but are restricted to "belts" or "patches" of forest, bush, or banana plantation, usually on the margins of watercourses, rivers, and lakes, and seldom far from water of some kind. In common language they may be described as "ordinary-looking sombre brownish or greyish-brown flies, varying in length from  $3\frac{1}{2}$  to  $4\frac{3}{4}$  lines ( $7\frac{1}{2}$  to 10 millimetres) in the case of *Glossina morsitans* to about  $5\frac{1}{2}$  lines ( $11\frac{1}{2}$  millimetres) in that of *Gl. fusca* or *longipennis*, with a prominent proboscis in all species" (19). In the resting attitude a ready



FIG. 107.—*Glossina palpalis* Robineau-Desvoidy. ♀ × 4  
West and Central Africa.

means of distinction from other blood-sucking flies, such as *Hæmatopota*, which might possibly be mistaken for them, is afforded by the position of the wings, which are carried flat, closed one over the other like the blades of a pair of scissors. The reproduction of tsetse-flies is extremely remarkable, for, instead of laying eggs, the pregnant female produces a single *full-grown* larva, which crawls away into some hiding-place and immediately turns into a pupa. This is of extreme importance, since, as will readily be seen, it renders any attempt to reduce the numbers of the flies by attacking the larvæ absolutely hopeless.

In addition to the eight recognised species of tsetse-flies characterised in my "Revised Synopsis," published in 1904 (20), a ninth species (from Angola) was described in 1905 by França under the name *Glossina becazei* (21). Only three specimens of this form, however, have so far been discovered, and it is probable that it will eventually prove to be

merely a sub-species of *Gl. palpalis*, which, in any case, it closely resembles. *Glossina palpalis* Rob.-Desv. (Fig. 107), the disseminator of *Trypanosoma gambiense*, the parasite of sleeping sickness, is about  $9\frac{1}{2}$  mm. in length, and the darkest of all the tsetse-flies. Its area of distribution, as shewn on my map, includes the river systems of West Africa, from Cape Verde to Angola, the Congo valley and basin, the northern and eastern shores of Lake Victoria, the entire circumference of Lake Albert, and the banks of the Nile from the latter to Gondokoro. As already mentioned, it is probable that other species of tsetse-flies are also capable of conveying the parasite of sleeping sickness, but this has yet to be proved by experiment. An important paper on "The Multiplication of *Trypano-*



FIG. 108.—*Auchmeromyia luteola* Fabricius, ♀  $\times 4$ ; and larva (natural size).  
Tropical and sub-tropical Africa; Nigeria to Natal.

*soma gambiense* in the Alimentary Canal of *Glossina palpalis*" has recently been published by Gray and Tulloch (22), and the internal anatomy of *G. palpalis* itself has been described and illustrated by Prof. Minchin (26). Mention should also be made of a paper on "*Glossina palpalis* in its relation to *Trypanosoma gambiense* and other Trypanosomes," which has appeared while these pages have been passing through the press (27).

The blood-sucking larva of *Auchmeromyia luteola* Fabr. (Fig. 108) another African Muscid, of which the perfect insect is incapable of sucking blood, was described and figured in 1904 by Drs. Dutton, Todd, and Christy, under the somewhat misleading name of "The Congo Floor Maggot" (23). For this species ranges from Nigeria to Natal, and is also found in British East Africa and Uganda. The perfect

insect, which is about 11 mm. in length, is of a pale yellow colour, with the distal half of the abdomen, except the tip, bluish-black. The larva, a dirty-white maggot about 15 mm. in length when full-grown, lives in the cracks in the earthen floor of native huts, and crawls out by night to fasten upon the limbs of sleepers and suck itself full of blood. While certain Dipterous larvæ are subcutaneous parasites in man and other animals, this free-living, blood-sucking form is at present entirely unique, and its discovery is consequently of extreme interest.

### Non-Blood-Sucking Flies

Space forbids us to devote more than a few lines here to those flies that, while incapable of sucking blood, are nevertheless, in some instances,



FIG. 109. — *Chrysomya macellaria* Fabricius. ♀ × 5.  
North and South America.

important agents in the dissemination of such diseases as cholera and enteric fever. In these cases the flies act as mechanical carriers of bacilli or other infective matter, and the effect is produced chiefly by the contamination of food. Information on this subject will be found in Dr. Nuttall's memoir (1), referred to above, and also in recent papers by Howard (24) and myself (25). The species concerned are those most closely associated with man, and of these the common house-fly (*Musca domestica* Linn.) is the most important.

Of the flies the larvæ of which are frequently found as intestinal or other parasites of the human body (Myiasis), *Chrysomya macellaria* Fabr. (Fig. 109), the larva of which is known as the "screw worm" in the United States, may be taken as a type. This species, a near relation of the well-known "green-bottle" flies (*Lucilia*), has a very wide range in North and South America, and is met with as far south as Argentina; the larvæ chiefly infest sores, but are also sometimes found in the nasal



and frontal sinuses. Another Muscid fly, of which the larvæ are subcutaneous parasites, is the African species *Cordylobia anthropophaga* Blanch., which coincides in range with *Auchmeromyia luteola* Fabr., to which it is also very similar in appearance. *Dermatobia norialis* Goudot, found in Central and South America, belongs to the *Estridæ*; its subcutaneous larva, which often infests man, has a bottle-shaped body, encircled by rings of black hooks.

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F E A

## TICKS

By R. I. Pocock, F.Z.S.

**Introduction.**—Records of the dread with which certain ticks are regarded by the natives of the countries infested by these parasites may be found scattered through volumes of travel, and repeated or extended in works on the natural history of this group of blood-sucking Arachnids. But a scepticism justified by the proneness of uneducated man to regard as venomous all repulsive-looking creatures of the insect kind, and strengthened by the negative results of experiment and by the knowledge that ticks have no poison-glands in the strict sense of the word, led to these reports being regarded with suspicion, or dismissed unconsidered as mere travellers' tales. In the latter part of the last century, however, interest in the question was revived by the discovery of the part played by mosquitoes in malarial infection, and by the definite association of a North American tick with the cattle disease known as "Texas" fever. Recognition of the economic importance of the last-mentioned discovery stimulated investigations which soon established a causal connexion between ticks and some previously puzzling maladies of domestic animals and birds; and within the last few years medical expeditions to tropical Africa have shewn that the bite of a species of tick, historically recorded as poisonous, is indeed followed in man by the "relapsing fever" of that country (*vide* p. 301).

It is especially worth bearing in mind that up to the present time all the ticks known to be harmful to mankind belong to the family Argasidæ, the members of which are for the most part parasitic upon domestic fowls. Only one species of Ixodidæ has so far been stated to be pathogenetic with respect to the human species; but the claim is as yet unsubstantiated, and amounts to little more than a suspicion. Since, however, it has been definitely proved that several species of Ixodidæ transmit pathogenetic sporozoa to dogs and cattle, which differ from each other in organisation, habits, temperament, and constitution as much as either differs from man, it would be unreasonable to suppose that man is exempt from the ill effects of similar or identical hæmozoic inoculation by ticks of this family. It is therefore important that medical men should have some knowledge of the habits and classification of these blood-sucking parasites.

Most of the genera and all the species and varieties mentioned or diagnosed in the following pages may be found described at length under the same or different names in the various papers by Neumann (29, 30, 31, 32, 33). The chief alterations here introduced are the resuscitation of *Curis*, the proposal of the new name *Alectorobius*, and the substitution of *Margaropus* for *Boophilus*.

### HOW TO DISTINGUISH TICKS

Ticks and mites, constituting the order Acari, are the only parasitic members of the class Arachnida. From other parasitic Arthropods, such as insects, they may be readily distinguished—(a) by the absence of antennæ; (b) by the presence of only two pairs of appendages connected with the mouth; (c) by the possession of four pairs of walking legs; (d) by the absence of segmentation and of any constriction separating the leg-bearing anterior portion from the legless posterior portion of the body; (e) by the position of the genital orifice in the middle or anterior half of the lower surface.

From other Acari, ticks may be distinguished—(a) by the presence of a median, usually sub cylindrical probe, beset with recurved teeth, which projects forwards beneath the mouth and between the palpi; (b) by the position of a conspicuous spiracular area above and usually behind the base of the last leg on each side.

### EXTERNAL ANATOMY

The dorsal surface is either membranous, leathery or thickly chitinised, or furnished with a chitinised plate only in front. Like the ventral surface it is marked with grooves or pits shewing the points of attachment of muscles. *Eyes*, when present, consist of simple lenses. In front of the anterior legs there is a movable sclerite, the *capitulum*, which bears the mouth parts. These consist of the median piercing probe covered with recurved teeth (*hypostome*), a pair of four-jointed *pulpa* on each side, and a pair of slender two jointed toothed *chelicera*, encased in a finely toothed membranous sheath, above. The term *rostrum* is sometimes applied to all these structures. It is by means of the teeth on the hypostome and chelicerae that the tick secures and maintains a hold of his host when sucking. Each *leg* consists of six main segments, known as *coxa*, *trochanter*, *femur*, *patella*, *tibia*, *tarsus*. The *tarsus*, bisegmented except on the first leg, bears apically a slender stalk which supports two claws, and often a membranous sucker beneath them. The anterior *tarsus* carries near its apex Haller's sense organ. On the ventral surface between the legs lies the *genital orifice*, and behind the last pair of legs the *valvular anal aperture*. Above and behind the base of the fourth leg is the *spiracular area*, upon which opens the orifice of the tracheal system.

### CLASSIFICATION OF TICKS

Ticks are referable to two very distinct families, the Ixodidae and Argasidae, which may be briefly diagnosed as follows:

- |                         |                                |              |
|-------------------------|--------------------------------|--------------|
| a Dorsal shield absent, | capitulum concealed from above | . Argasidae. |
| a Dorsal shield present | capitulum exposed from above   | . Ixodidae.  |

## Family Argasidæ

*Capitulum* concealed by an overlapping extension of the dorsal area, which has no chitinous plate. Integument fairly uniformly granular or coriaceous above and below. *Palpi* unmodified, first and fourth segments long, fourth not retractile, second and third not excavated internally. No sucker beneath claws, at least in adult. Sexual dimorphism slight.

The members of this family might appropriately be termed House Ticks. They are usually found in human dwellings, fowl-houses, dove-cots, etc., and are more commonly parasitic upon domestic poultry than upon cattle or other mammalia. They hide in crevices and dark corners during the day, and come out at night to feed.

The genera may be determined as follows:—

- a. Body produced laterally into a cariniform edge differing in sculpture from the rest of the dorsal and ventral surfaces.
  - b. A deep post-anal integumental groove . . . . . *Caris.*
  - b'. No post-anal integumental groove . . . . . *Argas.*
- a'. Body not laterally carinate; sculpturing of lateral area like that of the dorsal surface.
  - c. No movable sclerite on each side of the palpi . . . . . *Ornithodoros.*
  - c'. A movable sclerite on each side of the palpi . . . . . *Alectorobius.*

## Genus ARGAS Latr. (17)

Body flat or hollowed dorsally; elliptical or oval; its edges carinate. Dorsal integument shagreened or beset with fine granulations; the margins grooved at right angles to the edge; the muscular impressions forming radiating lines. No integumental groove behind the anus.

## Genus CARIS Latr. (17)

(= *Argas* of recent authors; see Neumann (29), p. 19)

Differs from *Argas* in having a conspicuous transverse slightly pro-curved groove just behind the anus. The type species *C. vespertilionis* occurs parasitically upon small European bats. The body is almost or quite as wide as long.

## Genus ORNITHODOROS Koch; Neumann (29), p. 25

Body generally oval, narrower in front than behind, anteriorly rounded or conically attenuated. Integument uniformly and coarsely granular throughout, without carinate differentiated lateral border. No movable plate on each side of the palpi.

## Genus ALECTOROBIUS nov.

Differs from *Ornithodoros* in having on each side of the mouth-parts an elongated movable plate or integumental flap capable of being folded beneath the adjacent palpus. Type species *A. talaje* Guérin (see *infra*, p. 196).

## Family Ixodidæ

*Capitulum* exposed, projecting from the anterior end of the body, and articulated to an excision of the anterior border of a firmly chitinated dorsal shield which covers the whole or a part of the upper surface. *Palpi* modified, first segment usually short, second and third longer and nearly always excavated internally, fourth minute and retractile. Tarsi with well-developed sucker beneath claws. Sexual dimorphism pronounced. *Male*: tergal area practically covered by the dorsal plate; no porous areas on capitulum; frequently well-developed ventral sclerites; integument scarcely distensible. *Female*: dorsal plate restricted to the anterior end of the body; a pair of porous areas on upper side of capitulum; no ventral sclerites; integument highly distensible.

This family is composed of ten genera classifiable in two groups, the Ixodæ and the Rhipicephalæ. Their differential characters may be tabulated as follows:—

A. *Females*. Dorsal surface with small chitinous plate at its anterior extremity; two porous areas upon the capitulum.

a. A transverse recurved pre-anal groove, the ends of which may surround the anus or extend back to the posterior edge of the body.

IXODÆ

Genera *Ixodes*, *Eschatocephalus*, *Ceratixoda*.

a'. No recurved pre-anal groove, almost always a distinct procurved post-anal groove approaching or meeting the two long genital grooves, diverging backwards from the genital orifice.

RHIPICEPHALÆ

b. Palpi relatively long and slender, second segment usually much longer than wide.

c. No eyes . . . . . *Aponomma*.

c'. Eyes present . . . . . *Hyalomma*, *Amblyomma*.

b'. Palpi relatively short, second segment about as wide as long, or wider.

d. No eyes . . . . . *Hæmaphysalis*.

d'. Eyes present.

e. Capitulum transversely oblong . . . *Dermacentor*.

e'. Capitulum hexagonal.

f. Spiracular area subcircular; pre-anal groove obsolete . . . . . *Margaropus*.

f'. Spiracular area comma-shaped; pre-anal groove present . . . *Rhipicephalus*.

B. *Males*. Dorsal integument thickly chitinated throughout. No porous areas on capitulum.

a. Ventral surface strengthened with five or seven chitinous plates; grooved as in females . . . . . IXODÆ

b. Third segment of palp long, acuminate . . . *Ceratixoda*.

b'. Third segment of palp short, apically rounded.

c. Palpi not excavated internally . . . *Eschatocephalus*.

c'. Palpi excavated internally . . . . . Ixodæ.

*a'*. Ventral surface soft or with two or four adanal plates

RHIPICEPHALÆ.

*d*. Ventral surface without adanal plates.

*e*. Fourth coxæ enormously enlarged . . . *Dermacentor*.

*e'*. Fourth coxæ not unusually enlarged.

*f*. Palpi short, second segment strongly angular externally . . . *Hæmaphysalis*.

*f'*. Palpi long, second segment not strongly angular externally.

*g*. No eyes . . . *Aponomma*.

*g'*. Eyes present . . . *Amblyomma*.

*d*. Ventral surface with one or two pairs of adanal plates.

*h*. Palpi long and slender, second segment twice as long as broad, or more . . . *Hyalomma*.

*h'*. Palpi short and stout, second segment at least as wide as long.

*i*. Spiracular area comma-shaped; external adanal plate when present usually shorter than internal . . . *Rhipicephalus*.

*i'*. Spiracular area subcircular; external adanal plate as long as the internal . . . *Margaropus*.

Genus IXODES Latr., Neumann (31), p. 108

(= *Euixodes* Neum. (34), p. 445)

Palpi of both sexes with second and third segments hollowed internally and ensheathing the hypostome; apex of the third segment rounded or blunt, not acuminate. *Male* usually with seven ventral plates, a small pregenital; a large genito-anal between the genital orifice and the anus, an anal which embraces the anus and extends posteriorly, a pair of adanals outside the latter, and usually a pair of epimerals external to the others and abutting against the coxæ and spiracular area; the latter oval. *Female* with three dorsal grooves posteriorly; spiracular area oval.

This genus contains a very large number of species, mostly of small size, and parasitic upon mammals, birds, and reptiles. None known to be pathogenetic.

Genus CERATIXODES Neumann (34), p. 115

*Female* like that of *Ixodes* and *Eschatoccephalus*. *Male* differing from that of these two genera in having the third segment of the palp long, acuminate, and far surpassing the point of articulation of the fourth. Further differing from male of *Ixodes* in having the second and third segments of the palp not hollowed internally.

*C. putus*, the only known species, lives parasitically on various sea-birds (Guillemot, etc.).

Genus *ESCHATOCEPHALUS* Frauent. ; Neumann (32), p. 290

(= *Haemalastor*, Neumann (31), p. 166)

Female like that of *Ixodes*. Male differing in that the second and third segments of the palp are convex and not hollowed internally. Legs usually long.

Several species found in caves and principally parasitic on bats.

Genus *AMBLIOMMA* Koch ; Neumann (31), p. 200

A pair of eyes on the margin of the dorsal plate. Mouth-parts long. Male without adanal sclerites.

A very large number of species, principally parasitic upon mammals, have been described.

Genus *APONOMMA* Neumann (31), p. 180

Very closely related to *Amblyomma*, but distinguishable by the absence of eyes. The species, few in number, are parasitic for the most part on tropical reptiles.

Genus *HYALOMMA* Koch ; Neumann (31), p. 283

Female practically indistinguishable from that of *Amblyomma*, males distinguishable by the presence of two pairs of adanal plates.

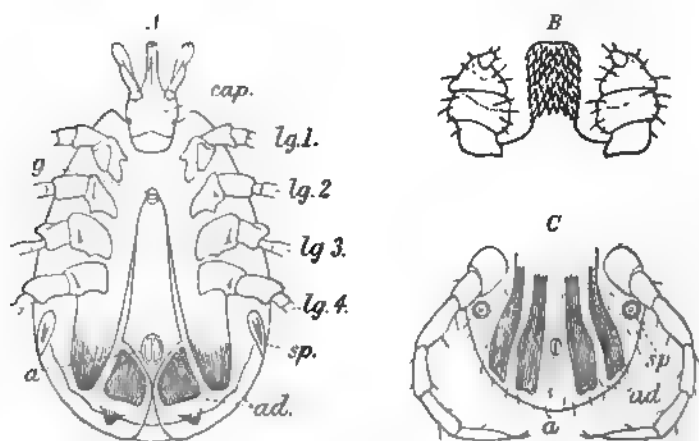


FIG. 110.—A, Ventral surface of male of *Hyalomma*. cap, capitulum, g, genital orifice; a, anus; ad, adanal plates, sp, spiracular area; lg, 1-4 basal segments of legs shewing bispinate anterior coxae. B, Palpi and hypostome of *Margaropus annulatus*, from below. C, Posterior extremity of *Margaropus annulatus*, male, from below; lettering as in A.

The small number of known species are parasitic upon mammals (cattle, etc.) and tortoises. None has been recorded as pathogenetic.



Genus *HÆMAPHYSALIS* Koch ; Neumann (30), p. 326

No eyes. Capitulum transversely oblong, about twice as wide as long. Palpi conical ; second segment externally produced into a strong angular or spiniform process. Spiracular area circular or comma-shaped. Coxa of first leg not bifid in either sex. Male without adanal plates, and with coxa of fourth leg of normal size.

Genus *DERMACENTOR* Koch ; Neumann (30), p. 360

Eyes present. Capitulum wider than long, transversely oblong dorsally ; palpi short and thick, the second and third segments hardly, if at all, longer than wide. Spiracular area comma-shaped. Coxa of first leg bispinate in both sexes. Male without adanal plates, but with coxa of fourth leg greatly enlarged.

Genus *RHIPICEPHALUS* Koch

( = *Eurhipicephalus* Neumann (34), p. 448)

Eyes present. Capitulum hexagonal. Palpi and hypostome short, third segment of palp armed below with a backwardly directed spine, second and third segments not thicker in the middle of their length. Anal groove and festoons present, coxa of first leg bidentate. Spiracular area oval, with pointed process. Male with one or two pairs of adanal plates.

A very large number of species, principally African, have been described. A few of them have been discovered to be pathogenetic.

• Genus *MARGAROPUS* Karsch (13), p. 96

( = *Boophilus* Curtice ; Marx ; Neumann (34), p. 448 ; *Rhipicephalus* Neumann (30), p. 407)

Differs from *Rhipicephalus* in having the external margin of the second and third segments of the palpi thicker towards the middle. Anal grooves and festoons obsolete. Spiracular area subcircular, without pointed process.

The one known species, described below, is the cause of "Texas" or "Redwater fever" infection in domestic cattle. It is widely distributed in temperate and tropical countries, and is represented by several more or less geographical varieties.

**DESCRIPTIONS OF THE BEST-KNOWN PATHOGENETIC SPECIES**

*Argas persicus* Fischer ; Neumann (29), p. 7 ; (32), p. 255

Body oval in outline, much longer than wide, narrower in front than behind ; yellowish, greyish, or reddish in colour. Dorsal surface convex, flat, or excavated above ; rugose and shagreened, the marginal sculpturing



formed of irregularly oblong areas impressed with a circular pit, and radially arranged with regard to the centre of the dorsum. Anteriorly there are two recurved series of eight or ten foveæ, and posteriorly a longer median series extending from near the centre to the posterior margin, and five or six shorter radiating series on each side. Smaller foveæ at the anterior and posterior ends exhibit a serial arrangement near the margin. Ventral surface with a median row of foveæ behind the anus, and from nine to twelve shorter radiating rows on each side. Marginally the foveæ form two or three series. In addition to these there are numerous scattered foveæ, especially anteriorly and posteriorly. Integument between the foveæ wrinkled. Spiracular areas semilunar transverse.

The fertilised and distended *female* measures up to 10 mm. long by 6 mm. broad, with a dorso-ventral thickness equal to about half the width. In the undistended state the rows of foveæ are represented by grooves. The *male* is about half the size of the female, and is flat dorsally, with the integument grooved as in the undistended female. The *nymph* resembles the male in general appearance. The newly hatched larva is a little more than 0.5 mm. in length, and about as wide as long. This species occurs in the southern and eastern countries of the Mediterranean area (Algeria, Syria, Persia); also in Russia, Turkestan, China, and Cape Colony. It attacks both poultry and human beings. In Persia the belief in the venom of its bite is prevalent and historical.

*Argas miniatus* Koch ; Neumann (29), pp. 9, 16 ; (32), p. 255

This species is very nearly related to *Argas persicus*, the only difference that Neumann [(32), p. 339] mentions being the less scattered arrangement of the granules towards the margins of the dorsal surface. The two resemble each other, and differ from the remaining forms of the genus in that the sculpturing of the margin takes the form of more regularly rectangular or oblong areas.

It occurs in Central America, the West Indies, the Southern States of North America, and also in New South Wales. It is said to have been taken on cattle, but appears most commonly to attack poultry, infecting them with spirillosis, which frequently proves fatal (see *Insect Life*, v. pp. 267 and 348, 1893 ; vii. p. 417, 1895).

*Ornithodoros moubata* Murray ; Pocock in Sambon (41), p. 222  
(= *O. savignyi* var. *cæca* Neumann (32), p. 256)

Body ovate, a little wider behind than in front, its anterior and posterior borders very widely rounded, with a lateral constriction behind the level of the third leg; yellowish-brown in colour when young, greenish-brown when adult, turning to blackish or reddish-brown in alcohol. Integument studded with mammilliform tubercles, crenulated at the base. Dorsal surface exhibiting three pairs of longitudinal grooves, each arising from a fovea, and running obliquely inwards and backwards; also with two short transverse grooves, one in front of the other, towards the posterior end. Above the base of the legs a longitudinal supracoxal

groove. Ventral surface with a deep pre-anal groove joining the supra-coxal grooves, and behind it three pairs of longitudinal depressions.

No eyes. Spiracular area semilunar in front, above the supra-coxal groove. Legs strongish, granular above, fourth leg half as long again as the first; tibiae and tarsi of first three pairs with three teeth on the upper side, a proximal, a submedian, and a chital, the chital tooth oval, the others rounded apically. Fifth leg similarly toothed, but the teeth smaller, the distal tooth of the tibia absent, and the second or the third very small, and in the proximal half of the segment. Length of extended specimen about 8 mm., width 6 or 7 mm.

This species is widely distributed in Africa from Uganda and German East Africa in the east, and Congo and Angola in the west, to Namaqualand and the Transvaal in the south. From the earlier described form, *O. moultoni*, which has been recorded from Somaliland, Abyssinia, German



FIG. 1. *O. montana*. A, dorsal surface of male; B, ventral surface of female.

East Africa, and the Congo, *O. montana* differs in the absence of eyes. In *O. montana* these organs are placed two on each side, one just above the base of the first leg, the other opposite the interval between those of the second and third pairs. *O. montana*, called *laho* in Uganda, *montana* in Angola, and *laupatu* on the Lower Zambesi, is much dreaded by the natives of these countries. Its bite is now known to be the cause of tick fever or relapsing fever in man in tropical Africa. In view of the close structural similarity between *O. montana* and *O. moultoni* and the overlap of their geographical range, it seems probable that the latter species will also prove to be instrumental in causing human spirochaetal infection.

In Mexico, Florida, and Texas there is an allied species, *O. turicata*, the bite of which proves fatal to fowls and harmful to human beings. Anteriorly the body is narrowed to a rounded point, the tibiae and tarsi of the legs are furnished above with three tubercles each, much smaller than those of *O. montana*, and there are no eyes. Another tick

*Alectorobius tulaje*, resembling *O. turicata* in general form, is regarded as a great pest to mankind in Mexico and in Columbia, where it is known as the "chinche." It also occurs in Venezuela and Chile, and is represented in South Europe by *A. coniceps* and in South Africa by *A. capensis*, which only differ from the typical form in points of minor importance.

*Dermacentor reticulatus* Fabricius; Neumann (30), p. 360

Male: dorsal surface variegated brown and white, sometimes one colour, sometimes the other predominating; the anterior elliptical area representing the dorsal plate of the female has a white edge and two brown stripes over the cervical grooves and one or more spots between them; the posterior area is marked with nine large brown blotches forming two procurved transverse rows and a central longer stripe; festoons brown and white; the white areas between the brown blotches speckled with brown over the punctures. The entire surface marked with fine and coarse punctures, the latter especially numerous at the sides; a marginal groove; palpi longer than hypostome; second segment expanded distally and curved above with a backwardly directed spike. Coxa of first leg strongly bidentate, the others with a single spine; coxa of fourth leg twice or thrice as large as that of the third. Length about 5 mm.; width about 2.5.

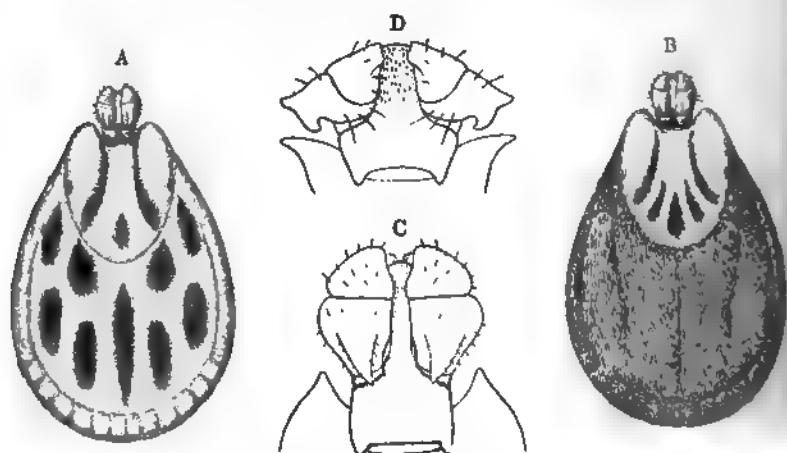


FIG. 112.—A, dorsal surface of *Dermacentor reticulatus*, male. B, dorsal surface of female (undistended). C, capitulum of *Dermacentor reticulatus*, from above. D, capitulum of *Hemaphysalis leachi*, male, from above, shewing the strongly angulate second segment of the palp.

Female: distended as much as 16 mm. long by 10 wide, with a shallow lateral constriction; dorsal plate speckled with white. Newly emerged female depressed, about as large as the male; dorsal plate similarly punctured; elliptical, extending back as far as the third pair of legs, coloured like the anterior portion of the dorsal plate of the neck;

eyes in the anterior half of its lateral border. Posterior area with a marginal groove, three longitudinal grooves and festooned edge. A membranous tooth on the dorsal side of the second segment of the palp. Coxæ spined as in the male.

Widely distributed in Europe, Asia, and America. It is the carrier of *Piroplasma canis* in Europe (Nocard and Motas), and has been thought to be responsible for the spotted or tick fever in man in the Rocky Mountains (Wilson and Chowning).

*Hemaphysalis leachi* Audouin : Neumann (30), p. 347

Male : dorsal plate yellowish-red, half as wide as long, narrowed anteriorly, covered with many fine punctuations ; a marginal groove and eleven posterior festoons. Palpi longer than hypostome, as wide as long, triangular, external angle of the second segment very prominent, with two processes ; inferior edge of third with a backwardly directed spike. Coxæ of all four legs with a short spine. Length, 3 mm. ; width, 1.5.

Female : When distended, oval in shape ; when recently emerged, depressed and much the same size and shape as in the male ; the dorsal scute oval, much longer than wide. Palp with second segment strongly produced, and spiniform externally at the process with a single backwardly directed spike. Coxæ of legs spined as in the male, but less strongly. Length of distended ♀ about 9 mm. ; width about 5 mm.

This species is especially abundant in tropical and South Africa, but has also been recorded from Algeria, Egypt, Sumatra, and N. S. Wales. It is commonly parasitic upon large carnivora, and, according to Lounsbury (20), conveys the hæmatozoon of biliary fever (*P. canis*) to dogs in South Africa.

*Amblyomma hebraeum* Koch

(*A. hebraeum* ♂ + *hassalli* ♀ Neumann (31), pp. 266 and 271)

Male : dorsal plate white, variegated with brown, a pair of short longitudinal stripes in front, sometimes meeting the ends of a median transverse procurved crescent ; on each side of the latter an outwardly curved stripe, and behind it three stripes, a median long one and a lateral short running forwards from the posterior submarginal groove. Legs brown, with white distal spot on all segments except first and last. Dorsal plate finely and equally punctured, with marginal groove continued posteriorly. Eyes flat. Coxa of first leg with two spines, the external longer ; of fourth leg with one spine, shorter than the segment. Length and width of dorsal plate about 5 mm.

Female : with dorsal plate brown or white, with brown covering the cervical groove and the ocular area as in the male. Dorsal plate almost as long as wide (3 mm.), subtriangular rounded behind, the posterolateral borders nearly straight, sparsely and finely punctured except on the lateral area, where the punctuations are numerous and deep. Eyes towards the anterior fourth of the plate, flat. Spines on coxa of first leg

about as wide as long. Length of distended female up to 24 mm.; width 15; newly emerged female a little longer than male. *Nymph*: brown like young female; 2 mm. long. Larva, 7 mm. long.

Widely distributed throughout tropical and South Africa. It transmits "heart-water disease" in sheep and goats in Cape Colony (Lounsbury (23)), where it is called the "Bont or Variegated Tick."

*Rhipicephalus appendiculatus* Neumann (32), pp. 270 and 336

Male differs from that of *R. bursa* principally in the following particulars:—Dorsal scute not quite covering the lateral portions of the body and leaving punctures of two kinds, some minute and numerous mostly anterior and continuing the marginal grooves; festoons narrow mostly twice as wide as long, the median continued into a conical caudal process, twice as long as wide. In front of the festoons three wide, short, longitudinal grooves. Ventral surface nearly hairless; external adanal spiniform sclerite. Length, 4 mm.; width, 2.6 mm.

Female differing from that of *R. bursa* in the nature of the punctation of the dorsal plate, which is more regularly oval; eyes larger and more posterior; porous areas of capitulum smaller. Occurs upon domestic cattle and buffaloes in South Africa, and infects the former with the sporozoon of African "coast fever" (Lounsbury (24)). In South Africa it is known as the "Brown Tick."

*Rhipicephalus bursa* Can. and Fanz.; Neumann (30), p. 391

Male: dorsal plate half as long again as wide, narrowed anteriorly reddish-brown, covered with many small, equal, and close-set punctures with eleven festoons, marginal groove, a short median groove, and two depressions on each side of it. Eyes above the posterior border of the coxa of the second leg. Palpi with postero-external edges of second and third segments angular; outer border of first segment concave giving a constricted appearance to the palpi. Lower surface beset with fine hairs. Adanal plate triangular, with equal sides, with transverse posterior border and anterior apex remote from the last coxa; external to it a beak spine. Coxæ of last three pairs with two spines. Length 4.5 mm.; width, 3 mm.

Female: distended, ovoid, nearly equally wide at the two extremities. Newly emerged oval, flat. Dorsal plate oval, with sinuous margin almost as wide as long; eyes near the middle of the margin; covered with many punctures of equal size; dorsal integument with marginal groove; three longitudinal grooves and posteriorly festooned; sometimes two additional grooves in front. Spiracular area oval, with posterior external prolongation. Coxæ of last three pairs of legs with a small antero-external spine and a small blunt posterior process. Length of distended female up to 17 mm.; width, 9; newly emerged female 4 mm. long by 2 mm. wide.

This species is distributed all over Africa, in S. Europe, the We

lies, and the Malayan Archipelago. It has been taken off horses, cattle, sheep, deer, and dogs. In Europe it conveys *Piroplasma ovis*, the cause of "heart-water" in sheep (Motas (28)).

*Rhipicephalus simus* Koch ; Neumann (30), p. 394

Male: dorsal plate nearly twice as long as wide, slightly convex, shining brown, a deep, strongly punctured marginal groove, and four longitudinal series of coarse punctures; lateral border and festoons unpunctured. Eyes flat. Lower surface finely punctured with scattered hairs; adanal plate triangular, its inner edge excavated, outer edge slightly convex, posterior edge oblique; a longish external spiniform process. Coxæ of last three pair of legs with two spines. Length, 4 to 6 mm., width 2·2 to 3·5 mm.

Female: uniformly brown, dorsal plate scarcely or not longer than wide, with numerous punctuations unequal in size, the finer not conspicuous; eyes flat, a little behind the middle of the border. Space between the porous areas of the capitulum equal to their diameter. Length of newly emerged female 6 mm., width 3 mm., distended 12 mm. long, 8·5 wide. This, like other members of the genus, is originally African. It is met with on large carnivora and herbivora, and, like *R. appendiculatus*, infects cattle with "coast fever" in South Africa, where it is commonly called the "Black-pitted Tick."

*Margaropus annulatus* Say ; Neumann (30), p. 407

Male: dorsal plate oval, narrowed anteriorly, widest opposite the stigmata, reddish-brown; beset with relatively large punctures; marked posteriorly with three grooves; festoons scarcely marked. Eyes often inconspicuous. Ventral surface hairy; furnished with two very large subequal, subsimilar adanal plates, on each side extending from the posterior coxæ far behind the anus. Coxæ of first leg with a blunt anterior process and posteriorly bifid; remaining coxæ with weak anterior spine. Length, about 2·25; width, 1·25 mm.

Female: elliptical, as wide in front as behind, uniformly coloured, with three integumental grooves. Dorsal plate small, longer than wide, rounded behind, its edges parallel anteriorly. Eyes small in the anterior third of the lateral margin. Genital orifice small, between the anterior coxæ and in front of the genital grooves. Length up to about 13 mm., width 7·5 mm.

This species is widely distributed south of about the 40th parallel of north latitude. It is parasitic in its adult stages upon large mammalia, principally domestic cattle.

The following varieties, differing from the type in characters of relatively small importance, have been described:—(1) Typical form from N. America and Mexico; (2) var. *winthemi*, Mexico, W. Indies, and S. America; (3) var. *argentinus*, Buenos Ayres; (4) var. *decoloratus* (Blue Tick), S. Africa; (5) var. *australis*, Australia; (6) var. *caudatus*,

Japan ; (7) var. *calcuratus*, S. Europe, N. Africa. *Piroplasma bigeminu* the sporozoon carried by this tick, produces the disease known among English-speaking people as "Texas" or "red-water fever," and as "Tristeza" in S. America.

### LIFE-HISTORY OF TICKS

The habits and development of *Rhipicephalus appendiculatus* have been worked out in detail (see, for example, Theiler (44)), and will serve to illustrate the life-history characteristic of many species of Ixodidae.

*Eggs and Oviposition.*—The gorged and fertilised female falls from her host to the soil, and after a short delay begins to lay her eggs in a sheltered spot. At the end of this operation, which may last several weeks, she dies. The eggs, numbering several thousands, are oval in shape and adherent. Development lasts about sixty days or less, according to conditions. The newly hatched and minute young, known as the *larva*, has only three pairs of legs and is without genital and spiracular orifice. With the hardening of the integument the larva gains strength and activity, and, climbing on to the herbage, waits, with outstretched legs for passing cattle. Having found a host, he becomes engorged in about six days, then drops to the ground, and lies dormant for about four weeks to prepare for moulting. The larval skin is then cast and the *nymph*, with four pairs of legs and spiracular orifices but no genital aperture, emerges. Its behaviour is like that of the larva; having secured a host in the same way, it becomes distended with blood in a week or ten days, then falls, and hides away for about one month, while the metamorphosis into the adult is being completed. The nymphal skin is then shed, and the mature tick appears with genital orifice and secondary sexual characters typical of the male or female. Both larva and nymph have the dorsal plate relatively larger than in the female but smaller than in the male.

The mode of securing a host by the *adult* is a repetition of that of the larva or nymph. After feeding for a day or two the sexes pair, the male for that purpose quitting his hold of the host to insert his mouth-part (? containing spermatophors) into the genital orifice of the female, while she remains the while with her hypostome and chelicerae firmly embedded. The male alters but little in appearance from feeding, but the female becomes enormously swollen before dropping to the ground, usually after about five days of gorging, to commence laying her eggs. The male may remain on the host for several months after the females have left.

Thus in *R. appendiculatus* each individual in the course of its existence must find a host three times, namely, in its larval, nymphal, and adult stages. This appears to be true of the majority of species. It is true for instance, of *R. simus*, of *Hemaphysalis leachi*, and very probably *Dermacentor reticulatus*; but not of all. In *R. bursa*, for example, the transformation of the larva into the nymph takes place upon the host, the larva remaining adherent while the moult is effected. The nymph



however, falls to the ground to undergo its final metamorphosis (Moults). This tick, therefore, must secure a host twice; first as a larva, second as an adult. From this we pass to *Marquardius univoltus*, in which the transformations both of larva into nymph and of nymph into adult occur upon the same beast. Once only, therefore, namely in its larval stage, has this species to find a host. Thus, a complete gradation illustrating the progressive evolution of parasitism may be traced backwards from *H. undulatus*, in which both moults are effected upon the host, through *R. imicola*, in which the first moult takes place upon the host and the second upon the ground, to *R. appendiculatus*, in which both moults occur on the ground. A further stage is exemplified by *Hyalomma aegyptium*, a common cattle tick, but one as yet free from suspicion of being pathogenetic, which is alleged to be parasitic only in its mature condition. Finally, there is the case of *Ornithodoros monticola*, in which the larval stage is passed within the egg shell. The rupture of the shell and the larval moult take place at the same time, so that the nymph in reality emerges from the shell (Dutton and Todd).

**Idiocy and Languidity.** Ixodidae are intolerant of dryness and soon die if kept without moisture, which is probably essential for respiration. On damp soil, however, they may survive a considerable time without feeding. Larva and nymphs of *Ixodes ricinus*, the English sheep tick, have been kept alive in damp moss for eighteen and nineteen months respectively. Some distended nymphs, after twelve months confinement, moulted into the adult stage and lived thereafter fifteen months, thus proving their capacity to exist without a fresh supply of food for two years and three months (Wheeler 45). Similar experiments upon tropical species have shown that larvae, nymphs, and adults may be kept alive unfed for several months in a damp environment. Megnin, indeed, had in his possession examples of *Aequi persicus* which were still alive after four years starvation. From these data it is evident that there is no pressing necessity to secure a host by ticks living in their natural surroundings, except in so far as they are saved thereby from destruction by insectivorous enemies or inimical climatic conditions. Feeding, however, at least in a great majority of cases, appears to be essential for growth and exuviation.

Strongly contrasted with the longevity which accompanies starvation and arrest of growth is the brief duration of life when feeding and growth are unimpeded. In the case of *R. appendiculatus* it appears that the total length of life from the hatching of the larva to the commencement of oviposition, after which the female dies, averages about seven weeks, a period probably not longer than that for which a larva or nymph might survive unfed under favourable conditions. Very much shorter lived is the South African variety of *M. univoltus*, which passes its whole life upon the same host, only three weeks being required from the hatching of the egg to arrival at maturity (Dixon and Speuill).

**Fertility.** Ixodidae are extraordinarily fertile. The number of eggs



produced by a female at a single laying has been variously computed at from several to twenty thousand [Barber (1)]. Since fertility is a measure of mortality, the two varying directly, it is evident that the destruction of these ticks at some period of their life-history must be enormous; and since it is probable that comparative safety is secured when a host has been found, it may be inferred that the dangers to which they are subjected fall upon them principally during development in the egg or during the quiescent stages preceding exuviation.

A marked exception in the matter of fertility is *Ornithodoros moubata*, which, according to Dutton and Todd, lays at most only about one hundred and forty eggs. This relatively low grade of fecundity is correlated with a mode of life and environment very different from those characteristic of the Ixodidæ. This animal lives in native huts in tropical Africa. It hides during the day in the dust and straw on the floor or in crevices in the muddy walls, and comes out at night to suck the blood of sleeping inmates. It does not appear to differ greatly in its habits from the common bed-bug (*Cimex lectularius*). By the nature of its habitat it is no doubt saved from a large percentage of the destructive agencies to which field ticks succumb.

*Stages of Growth and Infection.*—The stages of growth at which ticks are capable of giving rise to spirillosis or piroplasmosis vary in different cases according to the specific nature of the pathogenetic organism. In *M. annulatus* it has been proved experimentally and independently by Smith and Kilborne in North America, by Lignières in the Argentine, and by Koch in Africa, that when larvæ hatched from eggs of females fed or infected cattle are placed on healthy beasts, "Texas" or "red-water fever" appears in due course. On the other hand, in *Rhipicephalus bursa* both larvæ and nymphs hatched from eggs laid by females gorged on the blood of diseased sheep are incapable of infecting members of a healthy flock. Only the sexually mature individual is capable of conveying the malady. In this instance, as in that of *M. annulatus*, the sporozoa pass from the mother tick into her eggs, and thence to the larvæ; but whereas in *M. annulatus* they are transmitted by the larva into the blood of cattle, in *R. bursa* and *H. leachi* they remain quiescent and harmless through the larval and nymphal stages, only becoming pathogenetically active when the sexually mature condition is reached.

R. I. Pocock.

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# TROPICAL DISEASES



# TRYPANOSOMIASIS

By J. W. W. STEPHENS, M.D.

THE first case of human trypanosomiasis or trypanosome fever in a European was that described by Dutton. The peculiar symptoms exhibited by this case were—(1) Irregular patches of a congested or cyanosed character appearing on different parts of the body, the colour slowly returning after pressure; (2) an œdematous condition most marked on the face below the eyes, varying in degree from a scarcely noticeable swelling to well-marked puffiness; (3) an increase in the respirations to twenty or thirty, periodical accelerations occurring quite independently of any rise in temperature; (4) an increase in the pulse-rate from seventy to one hundred and twenty, the increase shewing no relation to the temperature; (5) an irregular intermittent temperature, with a few days of normal and subnormal temperature. To this list of symptoms must be added, in the light of subsequent investigation, enlarged glands. Though not noticeably enlarged in this classical case, yet in enlarged glands we have perhaps the most valuable means of making a certain diagnosis in the early stages at least, for later they appear to diminish again. For many, if not all, of the above symptoms may be absent, and we may be confronted with an illness in which practically the only definite sign is an evening rise of temperature. Trypanosome fever is caused by *T. gambiense*, and naturally, in making a diagnosis, one would turn to the blood examination. But here we are met with the difficulty, that for long periods the trypanosome may evade detection. It would appear from the observations of Thomas and Breinl that the trypanosomes, at least in natives, have a periodicity, i.e. they are absent for perhaps months, and then appear in the blood, perhaps only in scanty numbers for a day or more, to disappear again subsequently.

Enlarged glands are perhaps one of the earliest signs of the disease, and from the observations of Greig and Gray, Dutton and Todd, it appears that by puncture with a hypodermic needle the trypanosomes can almost invariably be found in the glands. In some cases certain of the symptoms of sleeping sickness are observed, e.g. apathy, feeble memory, somnolence, and pruritus. The disease is transmitted by one of

the tsetse-flies, viz. *Glossina palpalis* (*vide* p. 183); but other species also, at present unknown, are carriers.

**Diagnosis.**—The question will at first arise whether the case is one of an irregular temperature due to malaria. The absence of malaria parasites (provided no quinine is being taken), and the failure to control the temperature by quinine will negative this cause. In case trypanosomes cannot be found even in centrifugalised citrated blood, recourse should be had to gland puncture, *e.g.* the posterior cervical lymphatic glands.

**Prognosis.**—This is grave in the European, though apparently recovery may occur. The disease may terminate in sleeping sickness, or by intercurrent disease.

**Treatment.**—The only drugs that have been found to be of value are arsenic and an aniline body called by Ehrlich “trypanred.” Thomas recommends a meta-aniline arsenic compound called “atoxyl,” or the combined use of this and trypanred. The dosage of atoxyl for man is not as yet accurately determined; but Thomas recommends 5 c.c. of a 5 per cent solution to be administered twice a week, intravenously if possible. The dose should be increased gradually so long as no bad symptoms, *e.g.* headache and nausea, appear; and in all cases must be given in as high a dose as possible, and over extended periods, probably of a year or more. Trypanred may be given in the form of a pill (of 5 grains). The success of both these drugs, so far used only in the treatment of animal trypanosomiasis, is moreover only a partial one, but they are the only ones at our disposal. Trypanred, moreover, stains the tissues (of animals) during life, and the physician must decide between this objectionable property and the possibility of recovery in an otherwise almost certainly fatal disease. (For a further account of trypanosomiasis *vide* under Sleeping Sickness, and for a description of trypanosomes, p. 20.)

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## SLEEPING SICKNESS

By G. C. Low, M.B.

**SYNONYMS.**—Native names:—In Uganda, *Mongota* (*To nod*); on the Congo as *Yela Kwa Tula*, *Manungina*, *Lalangolo*, *N'tansi*, *or* *N'tola*; *Nelarane* (of the Wolofs); *Dadane* (of the Sereres); *Toruahebue* (of the Mendehs). European names:—*Sleeping drops*.

*negro lethargy, African lethargy, African meningitis, Maladie du Sommeil, Maladie des Dormeurs, die Schlafkrankheit der Neger, Malattia del Sonno, Doença de Somno, Enfermedad del Sueño.*

**Definition.**—An endemic disease of different parts of equatorial Africa, characterised by a gradually increasing lethargy, mental and physical degeneration, elevated evening temperatures, rapid pulse, progressive emaciation, tremors; after running an acute or chronic course it almost invariably terminates fatally.

**History.**—The first recorded account of this disease was published by Winterbottom in 1803 in a paper entitled “An Account of native Africans in the neighbourhood of Sierra Leone.” Later in 1868 Dumontier and Santelli independently wrote on the subject, and in the following year Guérin described cases seen in the West Indies among imported slaves. Corre, who personally investigated sleeping sickness in parts of Senegambia in the seventies, was the first to give a fairly accurate and complete account of the malady, but as his investigations took place before the more recent and important advances in neurology were made, his account of many of the symptoms is necessarily imperfect.

In 1891 Sir S. Mackenzie published the record of a case which was under his care in the London Hospital, and in 1900 Sir P. Manson (24) gave complete descriptions of two cases in Charing Cross Hospital, sent from the Congo by Dr. Grattan Guinness. The pathology of these latter cases was very thoroughly worked out by Dr. Mott, who first accurately described the pathological histology, and pointed out that the lesion was one of the nature of a meningo-encephalitis.

More recently a severe outbreak of sleeping sickness in Uganda has again attracted much attention to the subject, and many observers have lately advanced our knowledge of the symptoms and etiology of the disease very considerably.

In Senegambia Marchoux and Dantec, in Portuguese West Africa Cagigal and Lepierre, and a Portuguese Commission have all paid special attention to the etiology. Brodin on the Congo, Cook, Moffat, and Hodges in Uganda have also contributed papers on the subject, chiefly dealing with the prevalence and distribution of the disease in those parts.

In 1902 the Royal Society, in conjunction with the Foreign Office, sent out a special commission to Uganda to investigate the cause of the disease, and subsequent ones have followed this first one to continue the investigations and conduct further research on the spot. In 1903 the Liverpool School of Tropical Medicine sent out an expedition for similar purposes to the Congo, and their report was published in 1906.

**Geographical Distribution.**—The endemic area of sleeping sickness is limited to parts of equatorial Africa, and it has never been known to affect any one who has not at one time or another been resident within this area.

The scanty information formerly available referred principally to



places near the coast, but lately Sir P. Manson, from information from the Congo, has narrated accounts of the epidemic prevalence of sleeping sickness far in the interior of the continent. He says it is especially prevalent in the districts of Baol and Sin on the Senegambia coast, and is also found on the Rio Grande, at Sierra Leone, at Cape Mesurado in Liberia, on the Spice Coast, the Ivory Coast, the Gold Coast, at Fernando Po and other islands in the Bight of Biafra, in the Gaboon region, along the valley of the Ogooué, in the Cameroons, in the French Congo, and at St. Paul de Loanda, and other parts of Portuguese West Africa. It appears to be rare at the mouth of the Congo, but is extremely prevalent at many places on the lower reaches, particularly on the south side of the river, at Mbanza Manteka and Mukimbungu, for example; and also somewhat farther south, at San Salvador in Portuguese territory. It occurs intermittently as one advances up the river, and at Lukolula, 300 miles above Stanley Pool, it is said to be much dreaded by the natives, Glave remarking of this district that the bitterest malediction one negro can pronounce on another is *Owa na n'tolo*—"May you die of sleeping sickness." Recently Dr. Todd has shewn that the opening up of the country has caused an alarming spread of the disease towards the upper reaches of the river.

In 1900 Cook first discovered that sleeping sickness existed in Uganda, and since that date the disease has spread widely, keeping, however, more or less limited to the north shore of the Victoria Nyanza Lake. The epidemic apparently started in Usoga, and from this centre has spread to the north of Buddu in the west, and down to Kisumu, the rail-head in the east. Northwards, Cook has recorded cases from Kiadondo, but it does not seem to have spread much in this direction, as it is unknown in some of the northern provinces, and in Unyoro. But quite recently it has spread from Uganda to the districts about the Albert Lake. Southwards, in 1902 it had not crossed the Katonga river in the west, but had crossed Kavirondo Bay and extended down almost to the Kuya river in the east. Its centre of virulence has been in Usoga, in Chagwe, around Entebbe, the seat of the government, and also in all the islands adjoining the mainland, from the Sese group in the west to the Kavirondo islands in the east, some of those latter areas having been decimated by this scourge. So far it has not been reported in German East Africa, and it is unknown among the Nandi and Masai tribes who inhabit the territories of British East Africa east of Kisumu. The limits of the area of sleeping sickness extend, therefore, from Senegal in the north to San Paolo de Loando or even beyond in the south, the Congo river and Uganda also being affected. It would seem probable, therefore, that as our knowledge of Africa extends, this disease will be found endemic here and there throughout the basins of the Senegal, the Niger, the Nile, the Congo, their affluents, and in the hinterlands of most of the West Coast areas contained between the above mentioned limits. Its distribution in the endemic area is sometimes capricious. On the west coast of Africa and the Congo it appears to pick out a village here and there,

decimating the inhabitants, whilst neighbouring villages may be absolutely or relatively immune. Corre mentions that the garrisons of Joal and Portudal in Senegambia are exceedingly liable to the disease, and that when it breaks out in the neighbouring districts the villagers abandon their homes—so great are its ravages, and so much is it dreaded. The late Dr. Walfrideson stated that in Mukimbungu, a small village, several deaths sometimes occur in a week, and that few weeks pass without a death from this cause, whereas in other villages not very far away, the disease is known only by hearsay. There are also very large districts within the endemic limits where it rarely if ever occurs, for example, the Niger, parts of the Gold Coast, and Lagos.

In the days of the slave-trade a considerable proportion of the mortality among the slaves during the voyage across the Atlantic was said to be due to sleeping sickness. Moreover, we have evidence that the liability to the disease persisted after the slaves had landed in America; remaining dormant, as it were, to shew itself later, perhaps not until after several years of good health. Such a case, according to Sir P. Manson, occurred some years ago in England. A negro boy from the Congo died of the disease at a training school at Colwyn Bay, North Wales, although he had resided for three years in this country in good health before the symptoms declared themselves. Recently white people have died of sleeping sickness in England and Belgium, but in every case only after having lived for some period in an endemic area. The same applies to the negroes imported to the West Indies in the old days; only those who had lived in Africa acquired the disease, nor did it spread to the indigenous native; in Martinique, according to Guérin who studied the complaint there, it did not occur in negroes who had been resident on the island for more than ten years.

*Local Distribution.*—Walfrideson, writing of the disease as seen on the Congo, states that several cases may occur in the same families and among brothers and sisters, that a father and mother may die from the disease, and subsequently some of the children develop it after an interval. On the other hand, it may happen that the children suffer while the parents do not, but the commonest sequence of events is for individuals to be picked out singly in families exposed to the same conditions. Corre's testimony is to the same effect, and the same holds good for Uganda.

*Predisposing Causes.*—Age, sex, and occupation have little influence, either as regards liability or immunity. According to Walfrideson the age-incidence is mainly between five and fifteen, very old people—that is, above forty—appearing to be exempt. Corre places the period of greatest liability from the twelfth to the nineteenth year. In Uganda the disease is frequent in young children and middle-aged individuals. It is also seen, however, in natives well over forty. No age seemed to be exempt. Race is now known not to play an important part. Any one is liable to acquire sleeping sickness, but as the negro is more exposed to the cause, he gets it much oftener than the European, who

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More recently a severe outbreak of sleeping sickness in Uganda has again attracted much attention to the subject, and many observers have lately advanced our knowledge of the symptoms and etiology of the disease very considerably.

In Senegambia Marchoux and Dantec, in Portuguese West Africa Cagigal and Leprieux, and a Portuguese Commission have all paid special attention to the etiology. Brodin on the Congo, Cook, Mollat, and Hodges in Uganda have also contributed papers on the subject, chiefly dealing with the prevalence and distribution of the disease in those parts.

In 1902 the Royal Society, in conjunction with the Foreign Office, sent out a special commission to Uganda to investigate the cause of the disease, and subsequent ones have followed this first one to continue the investigations and conduct further research on the spot. In 1903 the Liverpool School of Tropical Medicine sent out an expedition for similar purposes to the Congo, and their report was published in 1906.

**Geographical Distribution.** The endemic area of sleeping sickness is limited to parts of equatorial Africa, and it has never been known to affect any one who has not at one time or another been resident within this area.

The scanty information formerly available referred principally to

places near the coast, but lately Sir P. Manson, from information from the Congo, has narrated accounts of the epidemic prevalence of sleeping sickness far in the interior of the continent. He says it is especially prevalent in the districts of Baol and Sin on the Senegambia coast, and is also found on the Rio Grande, at Sierra Leone, at Cape Mesurado in Liberia, on the Spice Coast, the Ivory Coast, the Gold Coast, at Fernando Po and other islands in the Bight of Biafra, in the Gaboon region, along the valley of the Ogooué, in the Cameroons, in the French Congo, and at St. Paul de Loanda, and other parts of Portuguese West Africa. It appears to be rare at the mouth of the Congo, but is extremely prevalent at many places on the lower reaches, particularly on the south side of the river, at Mbanza Manteka and Mukimbungu, for example; and also somewhat farther south, at San Salvador in Portuguese territory. It occurs intermittently as one advances up the river, and at Lukolula, 300 miles above Stanley Pool, it is said to be much dreaded by the natives, Glave remarking of this district that the bitterest malediction one negro can pronounce on another is *Owa na n'tolo*—"May you die of sleeping sickness." Recently Dr Todd has shewn that the opening up of the country has caused an alarming spread of the disease towards the upper reaches of the river.

In 1900 Cook first discovered that sleeping sickness existed in Uganda, and since that date the disease has spread widely, keeping, however, more or less limited to the north shore of the Victoria Nyanza Lake. The epidemic apparently started in Usoga, and from this centre has spread to the north of Buddu in the west, and down to Kisumu, the rail head in the east. Northwards, Cook has recorded cases from Kiadondo, but it does not seem to have spread much in this direction, as it is unknown in some of the northern provinces, and in Uuyoro. But quite recently it has spread from Uganda to the districts about the Albert Lake. Southwards, in 1902 it had not crossed the Katonga river in the west, but had crossed Kavirondo Bay and extended down almost to the Kuya river in the east. Its centre of virulence has been in Usoga, in Chagwe, around Entebbe, the seat of the government, and also in all the islands adjoining the mainland, from the Sese group in the west to the Kavirondo islands in the east, some of those latter areas having been decimated by this scourge. So far it has not been reported in German East Africa, and it is unknown among the Nandi and Masai tribes who inhabit the territories of British East Africa east of Kisumu. The limits of the area of sleeping sickness extend, therefore, from Senegal in the north to San Paulo de Loanda or even beyond in the south, the Congo river and Uganda also being affected. It would seem probable, therefore, that as our knowledge of Africa extends, this disease will be found endemic here and there throughout the basins of the Senegal, the Niger, the Nile, the Congo, their affluents, and in the hinterlands of most of the West Coast areas contained between the above mentioned limits. Its distribution in the endemic area is sometimes capricious. On the west coast of Africa and the Congo it appears to pick out a village here and there,



decimating the inhabitants, whilst neighbouring villages may be absolutely or relatively immune. Corre mentions that the garrisons of Joal and Portudal in Senegambia are exceedingly liable to the disease, and that when it breaks out in the neighbouring districts the villagers abandon their homes—so great are its ravages, and so much is it dreaded. The late Dr. Walfrideson stated that in Makimbungu, a small village, several deaths sometimes occur in a week, and that few weeks pass without a death from this cause, whereas in other villages not very far away, the disease is known only by hearsay. There are also very large districts within the endemic limits where it rarely if ever occurs, for example, the Niger, parts of the Gold Coast, and Lagos.

In the days of the slave-trade a considerable proportion of the mortality among the slaves during the voyage across the Atlantic was said to be due to sleeping sickness. Moreover, we have evidence that the liability to the disease persisted after the slaves had landed in America, remaining dormant, as it were, to shew itself later, perhaps not until after several years of good health. Such a case, according to Sir P. Manson, occurred some years ago in England. A negro boy from the Congo died of the disease at a training school at Colwyn Bay, North Wales, although he had resided for three years in this country in good health before the symptoms declared themselves. Recently white people have died of sleeping sickness in England and Belgium, but in every case only after having lived for some period in an endemic area. The same applies to the negroes imported to the West Indies in the old days; only those who had lived in Africa acquired the disease, nor did it spread to the indigenous native; in Martinique, according to Guérin who studied the complaint there, it did not occur in negroes who had been resident on the island for more than ten years.

*Local Distribution.* Walfrideson, writing of the disease as seen on the Congo, states that several cases may occur in the same families and among brothers and sisters, that a father and mother may die from the disease, and subsequently some of the children develop it after an interval. On the other hand, it may happen that the children suffer while the parents do not, but the commonest sequence of events is for individuals to be picked out singly in families exposed to the same conditions. Corre's testimony is to the same effect, and the same holds good for Uganda.

**Predisposing Causes.**—Age, sex, and occupation have little influence, either as regards liability or immunity. According to Walfrideson the age-incidence is mainly between five and fifteen, very old people—that is, above forty—appearing to be exempt. Corre places the period of greatest liability from the twelfth to the nineteenth year. In Uganda the disease is frequent in young children and middle-aged individuals. It is also seen, however, in natives well over forty. No age seemed to be exempt. Race is now known not to play an important part. Any one is liable to acquire sleeping sickness, but as the negro is more exposed to the cause, he gets it much oftener than the European, who

dresses in clothes and lives a more hygienic life in better surroundings. In the older days Corre heard of a case in the person of a European, and he saw it in a Moor. Chassaniol refers to a case occurring in the person of a mulatto. Recently many cases have been reported in Europeans, notably one of an English lady at the London School of Tropical Medicine, several from Uganda, including Lieut. Forbes Tulloch, who is supposed to have inoculated himself while performing an autopsy on a trypanosome-infected rat, a few in Belgium, and in 1905 a Frenchman in Paris.

**Etiology.**—Many different hypotheses have been brought forward to explain the genesis of sleeping sickness. The first observers believed that it might originate from emotional distress connected with negro slavery, while others considered it only a form of sunstroke or a variety of beri-beri, malaria, or scrofula. More recent opinions have connected it with an intoxication of food, animal parasites, bacteria, and protozoa.

**Food Intoxication.**—Some Portuguese investigators, and more recently Ziemann, have regarded sleeping sickness as a sort of intoxication—the latter considering it a manioc intoxication comparable to pellagra, a disease usually referred to the ingestion of diseased maize. There is little to be said in favour of this idea.

**Animal Parasites.** *Filaria persans*.—Sir P. Manson (23), remarking the singular correspondence between the distribution of the disease and that of *Filaria persans*, suggested that this nematode parasite might in some way be responsible as an etiological factor. More extended observations have shewn that this is not so. Areas such as British Guiana, where *Filaria persans* is very common, have no sleeping sickness, while, conversely, areas where sleeping sickness is abundant may shew no *Filaria*.

*Strongyloides stercoralis*.—The embryo of this worm was considered by Forbes as the cause of sleeping sickness; the parasite, according to Tessier, penetrated the mucous membrane of the intestines, and thus reached the general circulation, where it was retained in the cerebral vessels.

*Ankylostoma duodenale*.—Ferguson, on very insufficient grounds, believed that this parasite might be responsible for the disease.

**Bacteria.**—Cugigal and Lepierre announced in 1897 that they had isolated from the blood of a patient suffering from sleeping sickness a bacillus which, when injected into animals, reproduced the disease; this, however, was not confirmed later by Brault and Lapin. Subsequently, Marchoux stated that Frankel's diplococcus was the responsible agent, basing this view on the facts that at a post mortem examination of a case of sleeping sickness, complicated with pericarditis, the diplococcus was present in the exudate, and that in a second case, complicated by chronic rhinitis, the same microorganism was present. More recently Brodin, of the Bacteriological Laboratory at Leopoldville, described a bacillus as the cause. This organism was constantly present in the blood of all his patients, but was not agglutinated by the blood of patients suffering from the disease.

Following on this observation a Portuguese commission, sent out to Africa to study the disease, found a diplo-streptococcus constantly present after death, in the cerebrospinal fluid. This could also be found during life in the cerebrospinal fluid removed by lumbar puncture, and was considered to be the cause of the disease. According to cultural methods the organism is different from the ordinary streptococcus, the chief points of distinction being its slower growth on gelatin and the other usual media. In the following year Castellani in Uganda found the same organism. Out of 39 cases he grew it from the blood of the heart in 32, and from the liquid of the lateral ventricles of the brain in 30. During life, however, he found the germ more rarely, and stated that it was usually only present during the later stages; on this point he differed from the Portuguese commission.

*Proctor.* In November 1902 Castellani, on examining the cerebrospinal fluid of cases of sleeping sickness for organisms, detected the presence of trypanosomes in this fluid. Further examinations of different cases shewed the same parasite, and its presence was also detected in the blood. Col. Bruce, Drs. Nabarro and Greig, who formed the Royal Society's second commission for the study of sleeping sickness to Uganda, confirmed this discovery, and, working on the subject in detail, shewed that in every case of sleeping sickness, if properly examined, this parasite may be demonstrated. Further, they suggested that the trypanosoma of sleeping sickness was the same as the trypanosoma found by Drs. Forde and Dutton in the blood of a European on the Gambia, and that the disease which this latter gave rise to, namely trypanosomiasis fever, was really the first stage of sleeping sickness (cf. p. 32). More extended observations shewed that the distribution of sleeping sickness and the trypanosoma coincided absolutely for Uganda, and a species of tsetse fly, the *Glossina palpalis*, was found to be present abundantly in the affected areas, namely, the regions round the lake (cf. pp. 172, 183).

There is little doubt now that the specific cause of sleeping sickness and the agency by which it is spread have been discovered, though some minor points still remain to be settled. The trypanosoma explains perfectly the peculiar endemicity of the disease, the long incubation-periods that have been described, people leaving the endemic area apparently healthy and afterwards developing the disease; and also the observation that the complaint did not spread amongst the slaves in the West Indies.

**Pathological Anatomy.**—The chief pathological changes of sleeping sickness are found in the nervous system, and, as first pointed out by Dr. Mott, are essentially those of chronic meningo-encephalitis and meningomyelitis. Macroscopically the brain shows but slight alteration. The calvarium is not thickened, the dura mater is practically normal, and though seldom adherent to the skull may be united to the subjacent arachnoid. On removing the dura mater the pia arachnoid, often clear, is perhaps more usually somewhat opaque and slightly thickened, resembling ground glass; it may be adherent in places to the subjacent



brain, and on being stripped off brings some of the brain substance with it, while its vessels shew slight congestion. The subarachnoid fluid is usually of a pale straw colour, and is often increased in amount. In some cases it is slightly turbid—very rarely purulent, especially over the sulci and round the vessels in the membranes. On section the substance of the brain is moderately firm, and shews nothing abnormal, with the exception sometimes of excess of fluid in, and dilatation of, the lateral ventricles. The pituitary body, the pons, cerebellum, and medulla shew no gross lesions. The membranes covering the spinal cord are similar in appearance to those of the brain, and no lesions can be detected in macroscopical sections at different levels. The other organs also shew little morbid alteration. The heart is usually flabby, somewhat pale in colour, and there may be myocardial changes. Congestion and œdema of the lungs are almost constant. Patches of bronchopneumonia are common, and lobar pneumonia may be present. The liver and spleen do not present any gross changes attributable to sleeping sickness, though in malarial districts they are often enlarged, and shew the characteristic pigmentation of that disease. The kidneys, suprarenals, and pancreas are normal. The enlarged glands are a striking feature post-mortem. In the superficial areas their size generally varies from a bean to an almond, while the deep ones, especially the retro-peritoneal, are much larger, and are sometimes as big as a walnut. They are firm in consistence, but occasionally pus, the result of bacterial invasion, may be seen in those draining the area of the mouth.

*Microscopically*, definite and characteristic changes are always present in the nervous and other systems. Throughout the whole central nervous system, but especially at the base of the brain over the medulla and cerebellum, the pia-arachnoid is infiltrated with mononuclear leucocytes, a similar change spreading along the septa and affecting in varying degrees the perivascular spaces around the blood-vessels in the substance. The degree of perivascular infiltration varies considerably, and does not correspond to the symptoms; it is generally best seen in the pons, medulla, and cerebellum. The nerve-cells shew frequent pathological changes, the columns of Meynert, according to Dr. Mott, in some cases being disorganised, the outline of a great many of the pyramidal cells, large as well as small, being altered and irregular, indicating disorganisation and destruction. In another case described by the same author, in which hyperpyrexia was present before death, the Nissl bodies were neither visible in the cells nor in the processes, the whole neuron being uniformly stained by the dye instead of shewing the normal differentiation into achromatic and chromatic substances. The tangential and supraradial association fibres are usually diminished in number, and many are greatly atrophied. A diffuse sclerosis may be present in the cord, the axis-cylinders and medullary sheaths of the nerves shewing a well-marked degeneration in many of the cases. The arteries of the brain and cord do not exhibit endarteritis; the peripheral nerves are not degenerated; occasionally deposits of fat are present in the epineurium and endo-

neurium. As regards the other organs of the body similar leucocytic infiltrations round the vessels may be noted, the change being often best marked in the heart. Secondary changes such as occur in infectious diseases may also be seen, namely, cloudy swelling of the liver-cells and degenerative changes in the myocardium. The enlarged lymphatic glands shew a proliferation of lymphocytes, and the duodenum also shews a proliferation of the same elements with increase in the size of the lymphoid nodules. Sections of the brain and other organs stained by Loeffler's and Gram's methods often reveal the presence of cocci. In equatorial regions the liver and spleen are usually infiltrated with old or recent malarial pigment, and in other instances the peculiar cirrhosis due to bilharzial infection of the liver is met with. These, of course, are only concomitant changes, and have nothing to do with sleeping sickness.

**Pathology.**—Both the clinical history and the morbid appearances of sleeping sickness point to a chronic process, due, according to Dr. Mott, to a poison of micro parasitic or other source, which affects specially the lymphatic system, and in particular that portion of it pertaining to the central nervous system. He believes that the lethargy can be explained either by the action of a toxic agent, circulating in the cerebrospinal fluid, upon the vital activities of the neurons; or simply by the accumulation of lymphocytes around all the blood vessels interfering with the metabolic exchanges between the blood and the nervous elements; although the existence in such abundance of mononuclear leucocytes would rather indicate the existence and prolonged action of a noxious agent which itself would be capable of damaging the nervous elements.

The question now arises, can the trypanosome produce such a poison? So far experiments have failed to obtain a toxin from it, and a comparative study of the brains of animals dying from the effects of infections of different species of trypanosomes do not reveal similar lesions<sup>1</sup>. In these animals microscopic sections shew the dilated vessels packed with trypanosomes, whereas in the human cases it is almost impossible to find a single parasite. A chronic poisoning might account for the lesions, but why on the other hand should the acute cases, which die in a few weeks, have similar lesions? The general trend of opinion as regards the streptococci so frequently found in the cases is that they appear only as a terminal infection. It is open to doubt whether they are always terminal; moreover, the character of the infiltrations, if due to them, would certainly be polymorphonuclear and not, as it is, mononuclear.

More research on the subject is required, but as far as our present knowledge goes the trypanosome must be regarded as an essential factor in the disease, although how it acts in producing the pathological changes is yet unknown.

**Symptoms and Clinical Features.**—The symptoms of sleeping sickness begin very insidiously; the prodromal period is often greatly

<sup>1</sup> Recently Planmer states that the brains of rats that have been inoculated with the human trypanosomes have shewn the peculiar perivascular infiltration, and the brain of a monkey also inoculated with the human species is said to have exhibited similar changes.

prolonged, it may continue for months or even for one or two years—some say even longer. Such a sequence of events has been noted in Europeans with trypanosomiasis fever, definite symptoms of sleeping sickness only coming on at the end of a year or more. At this stage the diagnosis may not always be easy to the uninitiated. The natives, however, readily recognise the oncoming of the disease, changes in the former mental attitude of the patient being quickly noticed by his relatives. Quite early there may be slight puffiness of the face, a drooping of the upper eyelids, and a gradually increasing change in the facial aspect, a previously happy and intelligent looking negro becoming sad, apathetic, and morose. Next appears a disinclination to work, with a desire to sit about and rest more than usual, and at this time headaches and other transient pains, especially in the upper part of the chest, may be complained of. A tendency to fall asleep at unusual times, even in spite of strong efforts to keep awake, and a desire to lie and doze in the sun may also be noticed.

It is about this time, during these preliminary symptoms, that the patients are brought by their friends to see the doctor, and an ordinary casual inspection of such a case will reveal the following points. The appearance of the face is dull, heavy, and stupid looking. Questions are answered but slowly, the speech, when it does come, often being mumbling, slow, and thick. The gait is peculiar, the patient instead of lifting his feet in the ordinary manner pushes them along the floor as he advances. On asking the individual to put out his tongue a very fine fibrillary tremor is generally observed, and in some instances this may also be detected in the muscles of the hands. Glandular enlargements may be so prominent as not to require palpation to determine them; but in other cases they are smaller and less noticeable. A rough and dry skin is sometimes seen now, but by no means constantly. The most important aid, however, to the diagnosis of the disease in this stage is the careful study of the temperature and pulse, examination of which should never be omitted. The temperature is irregular, rising in the evenings to 101°, 102° F., or even higher, and falling in the morning to normal or even subnormal, the range often extending over 4° or more. The pulse is of a very low tension, with a moderate volume; the rate is accelerated, running up to 130 or 140 beats per minute, and varying between this and 90. A combination of those two phenomena in a patient in a sleeping sickness area should at once arouse suspicion. If the examination of a patient with those symptoms be interrupted, a careful observer may notice that his head nods, his eyes close; that he will probably sit down, and unless disturbed will remain in this state of absolute lethargy for a considerable time.

When once these well defined symptoms appear the disease runs an acute or chronic course, progressing, however, towards its ultimate fatal issue. Without treatment or careful attention, as of course is the case with the vast majority of those affected, the cases usually become rapidly worse. Often the healthy inhabitants of the villages or groups of huts





the sick to the bush, placing them there in small reed-huts, and except for providing them with food daily, leave them alone. They lie absolutely indifferent to everything around, asleep or half asleep, with eyes shut or half shut. When spoken to and they mumble in reply, but soon they merge again into their state of lethargy. The further course of the disease may be more fully studied if the cases be taken into hospital, properly looked after and fed. For the first few days or weeks a distinct improvement is noted; the patient gets up from his bed daily, sits about the hospital, sometimes even walks about a little outside and shows interest in life, especially at meal-times. Soon, however, the patient gets worse, he stays in bed more, muscular weakness and wasting become pronounced, tremors of a fine degree, most marked in the muscles of the tongue and arms, appear, and the drowsiness and lethargy increase. The patient remains in bed, and the symptoms of the final stages may then develop—the skin may lose its lustre, becoming dry and coarse, eruptions may come out, often accompanied with great itching, and in a commonly form, the motions are passed involuntarily, and dribbles from the mouth. The knee-jerks which were at first present become diminished, the tremors may become so excessive as to shake the bed on which the patient rests, choreiform movements or epileptiform seizures are sometimes seen, and rigidity of the muscles, often with flexor contractions of the legs on the thighs and of the muscles on the abdomen render the patient's condition a miserable one. The drowsiness which has been gradually deepening now passes into a coma in which eventually the patient cannot be roused, the temperature falls to subnormal, the body and extremities become cold and the patient dies in a state of complete coma, convulsions in the final moments ushering in the fatal termination.

This is the usual course of an ordinary acute case of the disease, the changes taking about a month or six weeks for completion. In chronic cases the symptoms develop more slowly, periods of deceptive improvement or even apparent cessation of the disease alternating with periods of advance till at last the final symptoms appear and carry the patient off.

**Symptoms in Detail**<sup>1</sup>—*The Temperature. Regular Course.*—The temperature is marked in typical cases by an evening rise and morning fall, the range often extending over 4° or more. The evening temperature varies from 100° to 104° F., and the morning temperature is usually about normal, or in some cases even lower. (*Figure Charts.*)

The regular type of temperature may go on for weeks, sometimes becoming distinctly irregular, and again keeping almost normal, with the exception of an occasional slight evening rise. This condition may persist for variable periods of time, often again to be followed by

<sup>1</sup>The description of the symptoms is largely taken from the "Report on Sleeping Sickness from its Clinical Aspects," by George C. Low and Aldo Castellani.—Royal Society, the Commission on the Sleeping Sickness, No. II., 1903.

the regular evening elevation and morning fall. A week or so before death the temperature almost always becomes subnormal, remains so during the whole day; this shews that the end is near. The rise of temperature is not accompanied by any special symptoms, there is no rigor, and no sweating, in fact, it is not uncommon to find a patient with a temperature of  $103^{\circ}$  F. walking about and apparently none the worse.

Variations from the typical temperature curves are from time to time met with, some charts, with the exception of one or two evening elevations, shewing a practically subnormal temperature throughout the course of the disease. Such cases may, however, be acute, and death may quickly supervene. In other instances the temperature may remain high for several days without shewing any marked morning remission. As a rule, however, after a few days, it reverts to the usual type. Careful study of any individual case of sleeping sickness will shew pyrexia at some time or other in the course of the disease. The ordinary temperature curve may be modified by intercurrent diseases, the most frequent being malarial fever; here the maximum is unusually high, often reaching  $104^{\circ}$  F. or higher, and the remissions are slight, sometimes never coming below  $100^{\circ}$  F. Parasites may then be demonstrated in the blood, and after the administration of quinine the temperature again reverts to its ordinary course.

*The Circulatory System.*—The study of the pulse is very important, especially in the early diagnosis of the disease. The frequency is very rarely below normal; it is usually somewhere between 90 to 130 beats per minute, but there may be great variations at different times of the day. The ratio to the temperature is inconstant, a very high frequency often being associated with a low temperature; but in the last stages a low frequency associated with the subnormal temperature is the rule. The rhythm is almost always regular in time and equal in force till the last stages, when some of the beats may be weaker than others; just before death, or even in some instances two days before, the pulse becomes imperceptible at the wrist. Dicrotism is uncommon, but may be present when the fever is high. The volume is always small, and is associated with a remarkably low tension, the vessel-wall exhibiting no thickening or other abnormalities in uncomplicated cases. There are no cardiac symptoms, palpitation, cardiac pain, dyspnoea, and giddiness all being absent. Physical examination reveals little except the rapid rate, and in some instances an increase in the transverse diameter and functional murmurs. Endocarditis and pericarditis were not met with in a long series of cases.

*The Respiratory System.*—The respirations, regular in time and equal in force, are always rapid, more especially in the evenings; they correspond fairly closely to the increased pulse-rate, and their number per minute is generally between 20 and 30. In the last stages of the disease Cheyne-Stokes breathing is common. The physical examination of the respiratory system in the first stages reveals nothing.



the later stages some engorgement and œdema of the bases of the legs, due no doubt to the recumbent position in bed, are commonly met with, and pneumonia or bronchopneumonic patches may appear.

*Alimentary System.*—In the early cases there is little to notice. In some patients the appetite appears to be slightly increased, and even in the advanced and completely bed-ridden cases nourishment is still taken readily. Dyspeptic symptoms are as a rule absent, and vomiting is never seen. The bowels are very often obstinately constipated. Labial herpes does not occur, but ulcerative stomatitis, usually slight, may be present, and in rare instances the gums become swollen and spongy. The tongue is flabby and usually covered with a dirty white fur; the pillæ on the dorsum may be prominent, and, in the last days of life, mucus accumulates in the mouth, saliva dribbles from it, and the breath is very offensive. Inspection of the abdomen often reveals a certain degree of bulging; the stomach is generally confined to its normal limits, though a certain amount of dilatation, due no doubt to the bulky vegetable diet, may be present. The spleen is enlarged, hard in consistency, though not tender, possibly from antecedent malaria. The liver is generally slightly enlarged, probably due in many instances to malarial hepatitis. True dysentery and pseudo-dysentery, due to the presence of bilharzia in the rectum, are common in countries where these diseases exist; they are only complications, and play no part in the cases of the disease.

*Integumentary System.*—Roughness of the skin, which has been considered one of the diagnostic features of this disease, is not by any means constant; in many cases, especially the acute ones, the skin is perfectly smooth up to the day of their death. The same must be said of eruptions which are not specially common, and when existing resemble those seen amongst the healthy natives of the district. The commonest eruption is a papulo-pustular one, and is most frequently seen on the dorsum of the hands, extensor aspect of forearms, and on the back, the individual pustules remaining isolated and shewing no tendency to coalesce. Pruritus is often present, and, as in other marasmic conditions, the skin may, especially in the chronic cases, become rough, scaly, and itchy. The circular erythematous rings seen on the white skins of Europeans suffering from trypanosomiasis are not visible on the black skins of natives. Forms of eczema and ordinary scabies are sometimes met with, especially in Uganda.

*Lymphatic System.*—A general enlargement of the lymphatic glands throughout the body is a constant feature in sleeping sickness, considerable variations in size existing, however, in different individuals. The superficial chains can easily be felt in the anterior and posterior triangles of the neck, in the submental and submaxillary regions, in Scarpa's angle, and in the groins. In emaciated individuals the deep abdominal glands are also palpable. Their size varies from a small bean to a hazel nut, or even larger; they are somewhat hard and firm in consistence, and do not become adherent to, or cause ulceration of, the adjacent skin.



In rare instances suppuration may attack single glands or groups of glands, those situated in the vicinity of the mouth being specially liable. In some localities the natives regard those swellings as the cause of the disease, and excise the glands both by way of cure and prevention. Recently, acting on Dr. Mott's suggestion, Drs. Greig and Gray in Uganda have shewn that trypanosomes can readily be found in the juice withdrawn from these glands by a hypodermic syringe, and they advocate this as an easy means of diagnosis in early suspected cases. Dr. Todd, following up this line of work, considers that every native living in an infected district with general glandular enlargement not due to any manifest cause, such as syphilis, tuberculosis, yaws, skin or scalp affections, due to cuts and wounds, lice, or seborrhœa, is almost certainly the subject of trypanosomiasis, even though apparently healthy. Before coming to such a diagnosis it is safer to explore the gland and demonstrate the presence of the trypanosomes, as general glandular enlargement—viz. palpable glands the size of an almond or upwards in the superficial areas—due to no apparent cause, are frequently met with in natives of India and other areas where trypanosomiasis and sleeping sickness are known not to exist.

*Nervous System*.—The dull apathetic look is one of the most characteristic points of the disease. The expression is heavy, and shews very little emotion. There seems to be a slight loss of intelligence, but memory is not impaired. When spoken to, a considerable interval generally elapses before the reply to the question is given. Speech is not, however, specially affected, there being no stammering nor slurring in the production of the individual syllables. Sleep, which has given its name to the disease, is in many cases not such a predominant factor as is generally supposed. It is perhaps questionable whether the amount of proper or physiological sleep is much in excess of that seen in an ordinary healthy native. A patient, if left alone and watched, is often seen to nod his head and close his eyes, but the slightest touch, such as stroking, or any noise, will make him open his eyes at once. Though the total amount of sleep in some individuals may be above the average, the usual condition may be better described as one of lethargy, indifference, and drowsiness, but it should be remembered that even this lethargic state may not be well marked in some cases, and that it may be entirely absent in others. The drowsiness in the later stages of the disease passes into coma, which gradually deepens till the patients can no longer be roused, and in this condition they die. Muscular attacks sometimes usher in the onset of the disease. Headache, chiefly occipital, indefinite pains in the chest and sometimes in the joints, especially in the knees and ankles, are sometimes complained of.

*Sensory Functions*.—These are at first normal, though even early there may be some hyperæsthesia of the trigeminal points. Touching or moving the patient, especially in those cases where flexor contraction or rigidity of the muscles of the neck are marked, causes pain, as is shewn by the patient crying out. General or local anesthetics are not met with.

the temperature sense is unimpaired, and the same may be said of the muscular sense.

*Motor Functions.*—Especially towards the end of the illness, when emaciation may be marked, the muscles frequently become wasted and flabby, though in the acute cases death often occurs without much loss of muscular nutrition. The motor power diminishes towards the end.

In many cases a certain degree of inco-ordination is distinct, and in a few instances Romberg's sign is present. Walfrideson described a case in which a staggering gait, with a tendency to fall forward, was a prominent symptom, while at the same time there was well-marked lateral nystagmus on looking to the left. The gait is characteristic, and is most aptly described as "shuffling," the feet not being raised from the ground, but being pushed forward.

Abnormal muscular movements are perhaps the most striking feature of the disease; fine tremor in the tongue is very constant, and a somewhat coarser tremor is also usual in the hands and arms, any purposeful movements, as lifting a cup to the lips, often increasing it. In a few instances tremor is found in the legs and muscles of the trunk as well, sometimes so excessive as to cause shaking of the bed on which the patient lies. In one or two patients in Uganda, who were ultimately proved at the necropsy to have had sleeping sickness, no tremors were visible during the whole course of the disease, but this is very unusual.

In the last stages rigidity is common in the muscles of the neck, and contractions of the legs on the thighs, and the thighs on the abdomen may at this time be extreme. Fits of an epileptic nature sometimes occur, either general or localised to a group of muscles. Paralysis is rare; it may, however, occur, one case shewing paralysis of the right side of the face, another that of one arm. Hemiplegia, or paraplegia were never seen in the Uganda cases, nor were choreic movements ever observed.

*Reflex Functions.*—The superficial reflexes are generally normal. The deep, exaggerated at first, afterwards become lost. There is never clonus. The organic reflexes are normal at first, but during the last weeks the motions are passed involuntarily, this, no doubt, depending on the weakness and inability to get out of bed rather than on any definite paralysis. Babinski's sign is not present.

*Lumbar Puncture.*—On performing this operation the cerebrospinal fluid escapes generally with increased pressure, though in some cases, few in number, the pressure is normal or even decreased. The fluid appears as a rule clear and colourless; in some instances it is slightly turbid. Albumin is found in traces, and the liquid usually reduces Fehling's solution. The leucocyte formula is mononuclear. Trypanosomes are always present, the best procedure for demonstrating them being to take 10 c.c. of the fluid, and after centrifuging this, to examine the deposit carefully.

*Special Senses.*—*Eyes.*—The pupils are equal and as a rule moderately dilated. They contract to light and during accommodation, the reactions

in some instances being sluggish. Nystagmus has been noted, but is very rare. Ocular paralysis is not seen, and the fundus and retina are in the vast majority of cases normal. Diffuse choroiditis has been noted in a European case of trypanosomiasis, who eventually died of sleeping sickness. The hearing, taste, and smell are unimpaired.

*Urinary System*.—Weakness of the sphincter vesicæ and consequent dribbling of urine may come on in the last stages. The amount of urine voided during the twenty four hours is at first normal, later it may be increased. When freshly passed it is clear, of a pale colour, with a low specific gravity, and has no special odour. In vegetable feeding races the reaction is alkaline, with abundant deposits of carbonates and triple phosphates. The excretion of urea is below the average, sugar is absent, and with the exception of a slight trace when the pyrexia is high there is no albuminuria.

*Sexual System*.—At first sexual desire is apparently not decreased, later, as the general nervous debility advances, it is lost. The same holds good as regards menstruation.

*Fæces*.—Constipation, as already mentioned, is very frequent. The stools of natives are generally hard, of greenish colour, and almost free from odour. Portions of undigested food, large shreds of vegetable tissues, and long fibres, are common in vegetable-feeding races. Microscopically, there are the usual innumerable micro-organisms, epithelial cells, crystals of triple phosphates, oxalate of lime, and occasionally Charcot's crystals. Ova of different parasites—Ankylostomes, *Ascaris lumbricoides*, *Trichocephalus trichiurus*, *Strongyloides stercoralis*, and *Schistosomum haematobium*—are very common in the Uganda cases. Amongst protozoan parasites *Trichomonas intestinalis* is also very frequently met with.

*Hæmopoietic System*.—Anæmia in varying degree is constant: the average number of the red blood-corpuscles per c.mm. being about 3,500,000. So many other hæmolytic factors are usually present, such as malaria and ankylostomiasis, that the count may be considerably complicated. When cyanosis exists just before death there may be an abnormal increase in the red blood corpuscles, an estimation of such a case giving 6,200,000 per c.mm. on the day of death. Commoner than this, however, is a gradual fall to 2,000,000 or under. The hæmoglobin is generally reduced in relation to the amount of the anæmia, the blood shewing all the characteristics of a well marked secondary anæmia. The leucocyte count shews no absolute increase from the normal until just before death, when a certain number of the cases get a well marked terminal polymorphonuclear leucocytosis. The large mononuclear elements are relatively increased. In areas where helminthiasis is common the blood of young subjects often shews a relative increase in the number of the eosinophil leucocytes.

*Complications*.—Bed sores, when emaciation is extreme, are common, but in hospital practice they may be usually avoided with ordinary care. They occur more frequently in chronic cases. Pemphigoid eruptions, boils, and other skin eruptions are not uncommon. In chigger-

infested countries the ulcerations, due to the neglect of treating this parasite, are very often seen. Epistaxis is rare, different forms of laryngitis are met with, and acute oedema of the glottis has been seen. Respiratory diseases, such as bronchitis, broncho- and lobar pneumonias, frequently precipitate the fatal termination. Malaria, true dysentery, pseudo-dysentery due to *Bilharzia haematobia*, and various animal parasites, all abound in Equatorial Africa, and at the necropsies their presence or the pathological lesions resulting from them are easily demonstrated.

**Course of the Disease.** The incubation period is uncertain, if the first manifestations of trypanosomes in the individual are taken as the starting-point of the disease, it lasts for years. In natives this is often difficult to determine, but in at least two Europeans the invasion of trypanosomes has been accurately noted, and in one of these definite symptoms of sleeping sickness did not develop until two years later. The rapid spread of the disorder in new regions would seem to shew that the incubation-period for natives may be shorter; but here again the difficulty of determining when the trypanosome first appeared amongst the tribe, and how long after that definite signs of sleeping sickness shewed themselves, must be considered. The period of incubation is probably variable; treatment and good hygiene retarding it. After the stage of incubation is over the symptoms begin insidiously, and the course of the disease is again variable. In Uganda the average duration seemed to be from four to eight months, but, not infrequently, in a case with practically no definite signs sleeping sickness would suddenly make its appearance and the patient die within six weeks of the first observation. Chronic cases seem, according to Dr. Todd, to be fairly frequent at the mouth of the Congo, and also occur in Uganda, the disease running a course of a year or more.

Remembering, then, that sleeping sickness may run an acute or chronic course, we may, for clinical convenience, recognise three stages. The symptoms of these are more or less definite, but merge insensibly into each other. The first stage is characterised by somewhat indefinite symptoms, vague pains, feelings of indisposition, slight degrees of drowsiness, and evening fever (an important point). The second stage may be designated as the stage of tremor, in which, with an increase of the early manifestations, tremors accompanied by other nervous phenomena appear. The third stage is characterised by emaciation and intense weakness. The patients become bedridden, lose control of their sphincters, emaciation becomes extreme, gradually deepening coma appears, the temperature falls to subnormal, and finally death supervenes.

**Diagnosis.**—The diagnosis from the clinical aspect alone may be difficult in the early stages, as the characteristic features of the disease (tremors, etc.) are generally absent. The most important point at this time is the evening rise of temperature and the increased pulse rate later, when the definite symptoms appear, there is little difficulty. Trypanosomes may be demonstrated by examining the blood or cerebro-spinal fluid, but Drs. Greig and Gray's procedure of puncturing one

of the enlarged glands offers an easier and quite as accurate a method. The trypanosomes may be so scanty in the blood that they may easily be missed, and it is usual, therefore, to centrifuge a large quantity of blood or cerebrospinal fluid.

*Differential Diagnosis.*—There are few diseases with which sleeping sickness may be confused, but some have from time to time been mentioned as resembling it.

*Beri-beri.*—This disease is a peripheral neuritis which comes on rapidly. In the wet form there is marked œdema, in the dry form, wasting of the muscles. In both forms the knee-jerk is abolished, and hyperæsthesia of the muscles is a prominent feature. In sleeping sickness these symptoms are absent, and the tremor, pyrexia, and lethargy at once distinguish the two diseases.

*Intracranial Syphilis and Tumours.*—Some cases of intracranial syphilis and tumours of the brain have been described, with a curious tendency to somnolence, the person dropping off to sleep while at work. Such cases, if occurring in the endemic area, might present difficulties, but in the former other evidences of syphilis would be present, and in the latter the usual definite symptoms of a cerebral tumour would be found. The evening temperature which is so constant in sleeping sickness would help to settle the diagnosis.

*Chronic Nephritis.*—Chronic nephritis with uræmic symptoms may present some superficial resemblance to sleeping sickness. Such cases have been sent into hospitals with the diagnosis of sleeping sickness, but examination shewed that the patient's urine was loaded with albumin, and that albuminuric retinitis was also present.

*Tubes and General Paralysis of the Insane.*—In some rare cases the pupils may react to light very sluggishly, and in the presence of Romberg's sign and the absence of the knee-jerk the question of *tubes dorsalis* must be considered. Strangely enough, though syphilis is common in Uganda, parasyphilitic manifestations are very rare. The tremor and evening pyrexia would help in the diagnosis, though it is quite possible both diseases might exist together. Perhaps the disease most closely resembling sleeping sickness is general paralysis of the insane, since symptoms of insanity are frequent in sleeping sickness. The temperature should help in a differentiation, and a search for the trypanosome would settle the matter in this as in the cases of the diseases already mentioned.

*Prognosis.*—The prognosis is always a grave one, and the disease almost invariably terminates fatally. Reported cures have generally proved to be only temporary ameliorations, but lately some cases have definitely been stated to have ended in recovery. This is possible in an early case of trypanosomiasis, but it is doubtful whether recovery can ever occur after undeniable symptoms of sleeping sickness have made their appearance.

*Treatment.*—Many drugs have been tried, but without any definite results. Iron, arsenic, and quinine, especially in the cases complicated



with malaria, produce a distinct but temporary improvement. Free purgation with magnesium sulphate or castor oil in order to counteract the persistent constipation gives considerable relief. The thermo-cautery and blistering the head with iodine have been tried, but with no appreciable benefit. Arsenic in increasing doses, cleanliness, good feeding, and proper attention may prolong life considerably, but a fatal termination comes sooner or later. Recently encouraging results have been obtained by Ehrlich and Laveran in the treatment of rats suffering from 'tagana' by large injections of arsenic and trypaned, an aniline dye, and by Dr. Todd in Liverpool with atoxyl. The success of these experiments has prompted the trial of those drugs in human cases, and recently several cases in Brussels have been said to have been cured by them. Such a statement is of course premature, as years must elapse before the question can be definitely decided; it is much more probable that the cases mentioned are only shewing temporary improvement, and will relapse again later, but still the observation is interesting as it is in all probability along these lines that a cure will come (cf. p. 208).

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## KALA AZAR

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**SYNONYMS.**—*Kala Dukh*, *Kala Jwar*, *Dum-Dum Fever* (Leishman), *Non-malarial Remittent Fever* (Crombie), *Tropical Splenomegaly*, *Cachectic Fever* (Rogers).

**Definition.**—Kala azar is a chronic and extremely fatal fever, of an irregularly remittent type, which occurs in epidemic form in Assam, and in endemic form in other parts of India and the tropics. It is characterised by great wasting, a progressive enlargement of the spleen, and a tendency to hæmorrhages and dropsical effusions. It is associated with the presence in the spleen, liver, and other situations of a protozoan parasite, the biological position of which has not yet been definitely determined.

**History.**—Kala azar has existed in the Assam district of India for many years, certainly since 1869, probably for long before that date. At all events in the early seventies it attained epidemic proportions, and gave rise to such a heavy mortality among the natives that villages were depopulated and whole districts thrown out of cultivation. Starting, apparently, in the district of the Garo Hills, the disease spread slowly up the river Brahmaputra, following the usual lines of communication and trade routes. Its progress was very slow; for instance, the distance of 100 miles between the Garo Hills and Gauhati was only traversed in seven years, and it has now reached the point at which the river emerges from the Eastern Himalayas into the upper part of the province of Assam. In its slow progress the disease, having fastened on a village, usually lingered there for a few years, and, after taking a heavy toll of the inhabitants, gradually died down, although sporadic cases were found to occur for years after the epidemic virulence had been exhausted. At present the disease still persists in Assam and is the cause of considerable mortality.

The Assam epidemic attracted much attention in India because of the high mortality it occasioned, and also from the divergent views expressed as to its causation. A wider interest has been created by the recent discovery of a new protozoan parasite which is found in practically all cases of the disease; and, further, because the same parasite has been found in cases occurring in many other parts of India and the tropics. There can be little doubt that these latter cases are also kala azar, for the symptoms and lesions are identical; the sole difference being the endemicity of the Assam disease, and the apparently endemic or sporadic character of the disease as met with in other parts of the world. In the following description the essential unity of the two forms is assumed, and, when it is necessary to differentiate between them, the Assam type of the disease will be referred to as the "epidemic" form and the cases now generally recognised elsewhere as the "endemic" form.

**Geographical Distribution.**—It is not at present possible to fix the limits of the distribution of kala azar with any degree of accuracy on account of the comparatively recent date of the discovery of the endemic form of the disease, and because the detection and identification of the parasite demand a certain degree of experience and technical skill. Although the recent epidemic in Assam has been confined to the valley of the Brahmaputra, it is in the highest degree improbable that this was the first appearance of the disease in India; probably some of the older epidemics, to which many allusions are found in Indian history, were of a similar nature. As regards the endemic form, cases have been reported from many other parts of India, from Madras, Calcutta and its neighbourhood, Dinapore, Ceylon, and Burma; while it has also been met with in China at Peking and Tonkin, in Arabia, Upper Egypt, Tunis, and Algiers. In most of these localities widening experience shews the disease to be by no means rare, and to be the cause of a considerable mortality.

**Etiology.**—The causation of this disease has in the past been the subject of considerable discussion and speculation, and very different views have been expressed by those who investigated it. Thus it has, in succession, been attributed to ankylostomiasis (Giles), to a severe and malarial form of malaria (Rogers (46), and, subsequently, Ross (51)), and to infection by the *Micrococcus melitensis* (Bentley (2)). Even at the present moment, although the recently discovered parasite would appear to be the cause of the disease, this cannot be said to be proved absolutely. The channels of entrance and of elimination are not definitely known, and the intermediate host, the existence of which is demanded by analogy, is still to be sought. In the presence of these important gaps in our knowledge of the life-cycle of the parasite any description of the etiology of the disease must be, for the main, speculative. There appears to be little doubt that the disease is spread by human intercourse, though not by direct "contagion" in its strict sense. Its communicability has long been believed in by the Chinese, and the history of the Assam epidemic shews that infection is carried to fresh villages or houses by new arrivals suffering from the disease, the first cases in a village usually appearing in the house in which



the new-comer resides. Although natives are the chief sufferers, it becoming increasingly evident that Eurasians and Europeans are frequently victims, especially of the endemic form; and there can be little doubt that many of the deaths of Europeans in certain parts of India which have been and are still recorded as due to malaria, chronic dysentery, and other complaints, are really the result of kala azar. The disease attacks individuals at any time of life, from infancy to old age, though the epidemic form was said to shew its heaviest incidence upon young adults. As regards seasonal incidence little can be said, because of the uncertainty as to the period of incubation and the widely differing conditions as to climate, temperature, moisture, rainfall, etc., prevailing in the countries where kala azar exists.

As regards the *elimination* of the parasite from the body, a fundamental point in the etiology of any parasitic disease, we have no certain knowledge; but there are several alternative methods which may be briefly discussed. (1) From the bowel. The presence of the parasite in the intestinal ulcers, and the intense degree in which the liver is usually affected, render it probable that they may at times escape in the faeces, but, although the probability cannot be denied, repeated and exhaustive search has failed to demonstrate their presence in the dejecta. It is possible that they may escape detection because they have undergone further development, such as takes place in artificial cultures; but no forms corresponding to these cultural forms have been seen, and such development in the intestine appears improbable, as artificial cultures rapidly die if contaminated with bacteria. (2) In the urine. The parasites, when found in the kidney, are confined to the endothelial cells of the smaller capillaries—chiefly the glomerular tufts—and have never been observed in the renal epithelium or the tubules. They have not been found in the urine, and they undergo no further development in this medium. (3) In the bronchial secretion. This is possible, but unlikely, since the parasites are but rarely found in the lungs, and then in extremely small numbers. (4) From cutaneous ulcers. This is certainly one method by which the parasites may escape, but, so far as our present knowledge goes, it is a route which can be employed in a few cases only. In many cases there is no history of cutaneous ulceration, and in Assam, where ulcers are common among the natives, Dr. Bentley (3) has examined ulcers in patients suffering from kala azar with absolutely negative results. The discovery of a parasite in Delhi boils, morphologically indistinguishable from the "Leishman body," must be remembered in this connexion, but the investigations of Capt. James (19) and others tend to shew that the two parasites are not identical. It is at least certain that they differ altogether in their geographical distribution, and that the local condition of Delhi boil is one which is never followed by the grave systemic disease known as kala azar. (5) The parasites may be eliminated in the blood. Their occasional presence in the leucocytes of the peripheral blood is referred to below, and it is possible that they might be present at a time when one of the hæmorrhages which are so frequent in this disease occurs. It

also possible that the parasites may be withdrawn from the blood by blood-sucking insects such as mosquitoes, biting flies, fleas, bugs, ticks, or small biting animals such as leeches.

*Artificial culture of the parasites*, withdrawn from the body by splenic or hepatic puncture, was first successfully accomplished by Major Rogers, and their development into free swimming flagellates has since been amply confirmed. The forms resulting from these cultures being described elsewhere (p. 52), reference will only be made here to some of the conditions of successful culture which appear to bear upon the pathology of the disease. Although the first stage of development has been observed in the spleen after death, further progress is only possible when the splenic or hepatic blood is kept from clotting by the addition of sodium citrate, and when the temperature of the culture is not allowed to exceed  $25^{\circ}$  C. No development whatever occurs at blood heat,  $37^{\circ}$  C. Major Rogers (49) reports that by acidifying his cultures with a little citric acid development occurs more certainly and more rapidly; but, in a recent case, I obtained as rapid development of flagellates without this addition as with it. Still, it is evident that a slightly acid medium, if unnecessary, is at least no barrier to the development of the parasites. All attempts to cultivate the parasites in water have failed. Contamination of the cultures with bacteria leads, as a rule, to the rapid death and degeneration of the parasites; but, in a case reported by Capt. Statham and myself, in which the immediate cause of death was a pneumococcal septicæmia, the pneumococci in the cultures died and the parasites thrived. Attempted cultivation in urine and in highly diluted fæces has failed. Subculture of the flagellates in freshly citrated human blood has been successful up to the third passage, but no further.

*Animal experiments* by inoculation or feeding, either with the spleen parasites or with the flagellated forms which develop from them in cultures, have so far proved completely negative. Among the animals which have been tried are monkeys, rabbits, guinea-pigs, rats, mice, fish, frogs, leeches, and insects of various kinds.

The possible *mode of infection* may now be shortly considered, in the light of the above facts. Of the three possible methods of inhalation, ingestion, and inoculation, the two latter need only be considered, as infection by inhalation appears highly improbable. As regards ingestion, many of the known epidemiological facts are consistent with the disease being water-borne, for instance Lieut. MacKenzie, at Dum-Dum, found that splenic enlargement caused by kala azar was common among natives who obtained their water-supply from the small "tanks" or ponds in the vicinity of their huts, such ponds being notoriously liable to urinary and faecal contamination; on the other hand, among the natives who made use of the pure tap-water supplied by the cantonment, the cases of splenic enlargement were almost entirely malarial. Against a water-borne hypothesis are the failure of cultivation experiments in water, and the rapid degeneration of the parasites when placed in water. There is, however, a further possibility that the parasites, reaching a water-supply

through fæcal or cutaneous elimination, may there find their alternate host in the shape of some water-organisms or animalculæ in which they may develop, and which, when swallowed by another individual, may cause infection. Some evidence has been brought forward in favour of disproving such hosts, but it awaits confirmation. Capt. Statham (58), however, as the result of his careful study of the distribution of the parasites in the tissues, considers it improbable that the gastro-intestinal tract is the original site of infection, and thinks the general evidence is in favour of inoculation through the skin. Inoculation may conceivably take place in several ways, by accidental inoculation through cuts, scratches, abrasions, or through the bite of some fly, insect, or small animal which may act as carrier or intermediate host of the parasite. Penetration through unbroken skin by way of the hair-follicles or the ducts of the sebaceous glands is a further possibility suggested by recent work on ankylostomiasis. The various alternatives are multiplied and complicated by our present ignorance of the form in which the parasite enters the body, whether as the oval "Leishman body," the flagellated cultivation form, the thin "spirillar" forms, which I have described as resulting from a process of unequal longitudinal fission of the flagellated parasites, or, finally, at some stage of development as yet unrecognised.

Discussion of the relative value of these and other hypothetical methods of infection is obviously out of place, more especially as we shall probably have definite information before long as to the facts of the case. Major Rogers' latest hypothesis (49) may, however, be mentioned; he considers that infection is carried from case to case by the common bed-bug; he has not yet succeeded in infecting bugs either naturally or artificially, but has cultivated the parasites successfully in the acidified and sterile blood withdrawn from the stomach of bugs which had been allowed to bite normal individuals. The other evidence he brings in support of his hypothesis is somewhat slight, but such a method of infection as he suggests is by no means improbable, and similar experiments with leeches, biting flies, or other insects may result in settling this most important question.<sup>1</sup> The rarity with which the parasites have been detected in the circulating blood, and their extreme paucity in the cases in which they are found, constitute the chief difficulties in believing that such a method of transmission could account for infection in all cases.

**Morbid Anatomy.**—Of the changes obvious to the naked eye after death from kala azar, those most frequently met with are the general emaciation and muscular atrophy, the enlargement of the spleen and liver, the presence of dropsical effusions, and ulceration of the large intestine. The post-mortem signs vary according to the stage of the disease at which death has occurred, and to the presence or absence of complications. The most important changes, however, can only be made

<sup>1</sup> Captain W. S. Paton has recently informed me that he has successfully infected bugs at Madras by allowing them to feed on kala azar patients in whose peripheral blood "Leishman bodies" had been found. In the gut of such bugs he subsequently found flagellated bodies resembling those which develop in artificial cultures of the parasite. A detailed account of Captain Paton's work will shortly be published.—W. B. L.

ed by the use of the microscope and the special staining methods which are necessary to demonstrate the presence of the parasite and its distribution in the tissues. The parasite itself the "Leishman body"—need not be described, as this has been done elsewhere (p. 50). The distribution of the parasite and the changes which are associated with its presence in the tissues have been closely studied, especially by Marchand and Ledingham, by Christophers, and by Statham; and the results and conclusions of these observers are in close agreement. In general it may be said that the parasites are almost invariably found in the cytoplasm of certain nucleated cells, seldom, if ever, free in the tissues or the blood. The nature of these cells is, naturally, a question of the first importance, and there is practical unanimity in regarding them as of endothelial origin. They are apparently the same cells as those charged with melanin granules in malaria, and the majority of them appear to have originally lined the walls of the smaller capillaries or lymphatics, and to have subsequently become detached from this situation. The powerful phagocytic properties of these cells are well known, and it appears probable that phagocytosis of the parasites plays an important part in the extension of the disease in an organ and in its spread from one organ or tissue to another. What appears to take place is somewhat of the following nature:—A parasite, however introduced into the body, gains entrance into, or is taken up by the phagocytic action of, an endothelial cell lining a small capillary or lymphatic, where the slowing of the current and the narrow calibre of the vessel favour such action. The parasite is not, however, destroyed by intracellular digestion within the endothelial cell but is able to live and also to multiply. This multiplication occurs by direct fission, and forms shewing all stages of division can be seen in such cells. As multiplication goes on the cell increases in size, and the nucleus is often displaced to one side: in smear preparations from an infected tissue, in which the individual cells can be readily studied, as many as 200 parasites may be counted in a single cell. This process of cell infection can be best seen in sections of an infected liver in which the endothelial cells lining the portal capillaries are seen in all stages of infection and the gradual detachment of the infected cell from the capillary wall is well brought out. Subsequently, the infected cells may rupture, either through the tension caused by their burden of parasites or by reason of a degeneration of the protoplasm, and the parasites thus set free are at once taken up by fresh cells and the process of intracellular multiplication repeated. The so-called "matrix," in which small groups of parasites are frequently found imbedded, is, no doubt, made up of portions of the protoplasm of the cell which originally harboured them. The detached and infected endothelial cells are probably unable to move far by reason of their large size and a possible loss of elasticity and power of accommodation to the narrow lumen of the finest capillaries; but the smaller cells or infected leucocytes are doubtless carried away in the blood or lymph currents, and it is probably in this manner that infection is spread throughout the body. The occasional occurrence of the parasites in the

leucocytes of the peripheral blood has already been referred to, but the rarity of their detection in this situation is remarkable in view of the intense infection which is usually found in the spleen, liver, and bone marrow.

The most obvious histological changes are found in those organs or tissues in which the parasites are most abundant, viz. the spleen, liver, and bone-marrow. The mesenteric glands are often intensely infected, especially when they drain an area of the bowel which has been the seat of ulceration. Less commonly, and in smaller numbers, the parasites have been found in the pancreas, kidneys, suprarenals, testicles, and lungs.

The *spleen* is usually enormously enlarged, and, if examined immediately after death, is of firm consistency and of a deep red colour on section. The capsule is somewhat thickened, and the trabecule hypertrophied. Microscopically, a condition of hyperplasia is found, and the organ is seen to be gorged with blood. Black malarial pigment is sometimes seen, but is frequently absent. By deep chromatin staining the parasites may be seen, usually in enormous numbers, lying in mononuclear cells of various sizes. These infected cells are as a rule somewhat irregularly distributed throughout the splenic pulp, some areas being much more intensely infected than others, while the Malpighian corpuscles are usually free from infected cells.

In the *liver*, although enlargement is less constant and less in proportion to its normal size than in the case of the spleen, there is usually profound histological change. The appearance on section varies, being either dark brown or shewing a mottled brownish or yellowish appearance; a "nutmeg" condition is not uncommon. Microscopically, the interlobular capillaries are usually dilated, and the infected cells, described above, are seen in them in large numbers, either free or partially attached to the walls of the vessels. In most instances these infected cells are more common in the portal than in the hepatic zones of the lobules. A moderate degree of cirrhosis is sometimes met with, but the principal changes are seen in the hepatic cells, which often shew signs of atrophy and nuclear degeneration, while in some I have seen advanced fatty change; but the parasites have never been seen in the hepatic cells. Black or yellow pigment may be found, but neither form is invariably present.

The *bone-marrow* is usually intensely infected with the parasites, which here also occur in mononuclear cells of the same nature as those in the spleen and liver. The yellow marrow is usually converted into red marrow, and is softer and more diffuent than usual. Histological change is not marked in the other organs, in which the parasites are only found in small numbers, but here also they occur in the cytoplasm of cells similar to those described.

There remain two situations in which the parasites have been found, namely, in ulcers of the skin and in ulcers of the intestine, and the etiological importance of their occurrence in these ulcers will be obvious.



*Intestinal ulceration* is not uncommon in kala azar; and although in some cases the ulcers may be due to dysentery, in others they appear to be an integral part of the disease. The colon and sigmoid flexure are the most frequent sites of these ulcers, and a great variety of appearances have been described in different cases, varying from small petechiae shewing no superficial erosion, to large ulcers extending over a considerable area of the gut. Cicatrices of old ulceration are common, and both thinning and thickening of the gut have been found. In view, however, of the uncertain causation of the older ulcers in some of the cases which have been described, it is not at present possible to define the typical features of the specific ulceration of kala azar. When the parasites are found in these ulcers they are, as usual, intracellular and not very numerous. In a few cases also the parasites have been found in small papules and ulcers of the skin, and also in a lymphatic gland draining the area of skin affected by one of these ulcers. Their presence in cutaneous ulcers is, however, by no means common, as many have been searched for them in vain. Their occasional presence is of importance from two points of view—first, as suggesting a possible channel of elimination of the parasites from the body, and secondly, as raising the question of the identity or non identity of the kala azar parasites with those found in Delhi boils by J. H. Wright (cf. p. 55).

**Symptomatology.**—The early symptoms of kala azar are neither well known nor well defined. From its chronic course, often lasting from one to two years, and as cases are not usually recognised till the disease is established, the details of history usually depend on the statements of the patient or his friends; there are few cases on record which have been followed from the onset by a medical man. Matters are further complicated by the liability of those dwelling in tropical countries to malarial and other affections with symptoms that may thus be unintentionally included in any verbal account of the early stages of a case of kala azar. The literature of the Assam epidemic is also somewhat confusing in this respect, inasmuch as the writers, in most instances, held views of causation which have since proved fallacious, and have probably described as symptoms of kala azar features which were, in reality, attributable to the disease with which they believed it to be identical. In this way symptoms of malaria, ankylostomiasis, and Malta fever have in turn been included in the older descriptions of the disease. Bearing this in mind, the writings of Ross (51), Giles, Bentley (2), Rogers, James, and others have been largely drawn upon in the following description.

The *period of incubation* is very uncertain, but it is probably of considerable duration; from certain cases observed by Major L. Rogers it would appear to vary from three weeks to several months after exposure to infection. Until our knowledge of the mode of infection is more definite this point cannot be definitely established. The first symptom noted appears to be fever, which may be either intermittent or remittent, and is occasionally preceded by a rigor; in the absence of a blood examination it cannot be distinguished from an attack of malaria. Dr Bentley

has described initial symptoms of a gastro-intestinal or dysenteric nature, and at times nothing special has been noted by the patient except steadily increasing debility and the gradual appearance of the more definite symptoms which manifest themselves later in the disease.

The duration of the initial attack of fever is variable, ranging from two to six weeks; during this time the spleen, and frequently the liver also, begin to enlarge, the enlargement being usually accompanied by a considerable amount of pain and some tenderness on palpation. There are few records of the temperature curves of the initial fever, but it appears, as a rule, to be irregularly remittent. When this attack subsides there is a general amelioration of the symptoms; but, after a longer or shorter interval, during which the temperature is normal and the patient feels well, another attack of fever, resembling the first, occurs, this in turn disappears, only to be followed once more by fresh attacks, the intervals of apyrexia becoming shorter and shorter, until they merge in the condition of continued fever which constitutes the second stage of the disease.

During this first stage of successive attacks of fever the enlargement of the spleen and liver becomes more accentuated, and these organs no longer return to their normal size, as usually happens after the earliest attacks, while the patient begins to shew evidence of the drain on his strength in the appearance of anemia and gradually increasing debility and wasting. The duration of this stage averages one to three months, but it varies within wide limits, in common with the subsequent stages. The condition of continued fever which constitutes the second stage lasts, as a rule, from seven to twelve months, and merges by degrees into a third or final stage of cachexia in which the temperature may fall to normal or below it, with occasional conflagrations of high fever of a very irregular character. During the second stage a condition of profound cachexia is gradually established, and the sufferers are usually greatly emaciated and debilitated. This progressive lowering of the vital powers may end in death from asthenia, but death more commonly results from one of the complications or terminal affections, against which the enfeebled constitution of the patient can make no stand.

Although the general course of the disease follows the lines described above, the greatest variations are met with in individual instances, and cases may either run a chronic course lasting two years or more, or may, though rarely, prove fatal within two months of the first appearance of the symptoms.

The following individual symptoms of the disease may be taken as common to both forms—the epidemic and the endemic—since, as far as our present knowledge goes, there is no essential difference between them.

*General Condition and External Appearance.*—Once the disease is established there are marked signs of the progressive anemia and muscular atrophy. The swollen state of the spleen is frequently visible to the eye as an abdominal tumour which may extend beyond the

umbilicus. In children, especially, the abdominal distension thus caused forms a striking contrast to the emaciated limbs. The skin becomes dry and furfuraceous, and, in natives of India, is often darkened from the normal chocolate colour to a blackness resembling that of an African. This blackening is well known to the natives, and is the origin of the name "Kala Azar," or black sickness. It is not, however, due to the deposit of pigment in the skin, as in malaria, but to trophic changes. In Europeans an extraordinary earthy pallor of the skin is common, often of a yellowish or greenish tinge, which, once seen, is, I think, very suggestive. The hair is apt to become dry and brittle, losing its natural gloss and elasticity, and frequently falls out in quantities.

The extreme emaciation commonly seen in those who survive to the later stages of the disease is not, however, invariable, cases being met in which the body appears to be well nourished even shortly before death.

*Fever.* This, the earliest and most frequent manifestation, is also one of the most variable as regards continuity, height, and type. The general course has been indicated above in describing the three stages into which the disease may be divided. That of the initial stage is, as a rule, remittent, with an upper limit of 103-104 F., but, once the second stage of continued low fever is reached, it follows a very irregular type, sometimes remittent, sometimes intermittent; while, as a rule, the daily maximum does not exceed 101 F., and in this respect shows a certain amount of regularity. At times severer attacks occur, and the charts may be further complicated by intercurrent attacks of malarial fever or by inflammatory complications. It has been noted that at this stage the patients often appear to have acquired a certain tolerance of the fever, and may be ignorant that their temperature is two or three degrees above the normal. Major Rogers (48) further notes that by two-hourly or four-hourly observations a double or even a treble rise may be noted in the twenty-four hours, an observation to which he attaches diagnostic importance. In the cachectic stage the extreme irregularity of the temperature is its most distinctive feature. High remittent fever may be present at times with intermissions of apyrexia, during which sub-normal readings are very common.

The *spleen* is almost invariably enlarged, and at times attains enormous dimensions, half filling the abdomen and rivalling the liver in size. In the early stages the swelling is often accompanied by pain and tenderness on palpation. The organ is often subject to great fluctuations in size, and rapid diminution of bulk has been noted to coincide with a severe attack of diarrhoea. The degree of splenic enlargement does not appear to bear any distinct relation to the severity of the disease.

The *liver* is also frequently enlarged, but not so constantly as the spleen, nor to such a degree; it is seldom found to extend more than one or two fingers breadth below the costal margin. Pain is complained of at times, but is neither constant nor severe. A moderated degree of jaundice has been noted, but this is exceptional.

Some form of *oedema* may occur at almost any stage of kala azar,



and is seldom absent from the history of a case. It is, as a rule, slight, and confined to the feet and ankles, but may, in the later stages, take the form of ascites or effusion into the pleural or pericardial cavities, while death occasionally results from oedema of the lungs. Transitory oedemas of various regions of the face, trunk, or limbs are common and have been a feature in the history of every case which I have examined.

*Hæmorrhages* may occur at any stage of the disease, and may take the form of epistaxis, bleeding from the gums, hæmatemesis, or melæna, while cutaneous hæmorrhages, in the form of purpuric eruptions or subcutaneous extravasations, are very common. This tendency to oedema and hæmorrhage is conceivably associated with the deficient coagulability of the blood that has occasionally been observed. Intestinal hæmorrhage may be due to the specific ulceration of the bowel, but the frequency of true dysentery and ankylostomiasis in kala azar countries must be borne in mind, as possibly complicating the case and causing the hæmorrhage.

*Changes in the Blood.* The condition of the blood varies with the stage of the disease. As already noted, a progressive anæmia is established as the attack advances, but the loss of red cells is less than the appearance of the patient would suggest. The average number of red cells is 3.4 million per c.mm., and it is rare to find them reduced to 2½ millions. Nor is the "colour index" much reduced, when allowance is made for the low normal value found to exist in the Assamese. Abnormal red cells and nucleated reds are rare. Changes in the numbers and relative proportions of the leucocytes are, however, much more frequent and important. Early in the disease a moderate leucocytosis may be found, but this soon disappears, and a marked leucopenia is established as the disease progresses, the polymorphonuclear leucocytes being chiefly in default. Major Rogers (50) found that in the later stages, during apyrexial intervals, the total number of leucocytes seldom exceeded 1000-2000 per c.mm., while they were occasionally as low as 700-800. As regards the relative proportions of the different leucocytes two features are frequent, a relative and absolute decrease of the polymorphonuclear and a relative increase in the numbers of the large mononuclear or hyaline cells. This point is of interest in view of the importance which Major Rogers and others have attached to such a mononuclear increase as affording evidence of malaria. Although kala azar patients may and do suffer from intercurrent attacks of malaria, there can be no doubt that in these cases, the relative mononuclear increase is attributable to the severer disease; and it is not improbable that many cases of so-called "malarial cachexia," in which such a relative increase has been taken as additional evidence of their malarial nature, have, in reality, been unrecognised cases of kala azar.

A searching examination of films of peripheral blood may at times reveal the presence of the recently discovered parasite—the so-called

"Leishman body" or "Leishman Donovan body"—in the protoplasm of a leucocyte. Unfortunately, from the point of view of diagnosis, this is

a very rare occurrence, still, they should always be searched for, since, if found, the necessity for the performance of splenic or hepatic puncture, in order to establish the nature of the case, would be obviated. The chances of success are best when the temperature is high ( $102-103^{\circ}\text{F}$ ), but parasites are so rare that hundreds of leucocytes may be searched before a single individual is detected, and this, in the presence of so pronounced a leucopenia, is no light task. Collection of a larger quantity of blood [0.5-1 c.c.] in a capsule, and the addition of 5 per cent of sodium citrate solution to obviate coagulation, facilitates the search, the corpuscles being centrifuged, or allowed to form a sediment and the upper layer of cells pipetted off for examination. It is very doubtful if the parasites are ever free in the plasma, except by reason of the rupture of an infected leucocyte in the process of preparing the film.

Major Donovan (16) has described endoglobular forms of the parasite in the red cells of the peripheral blood, but his observation, although endorsed by Laveran, has not been confirmed by other observers, and, in the coloured plates which he has published, these forms shew little resemblance to the parasites as seen in the spleen, and are more suggestive of the young ring forms of malaria parasites (cf. p. 51).

No very constant symptoms have been referred to the *nerveous* or *respiratory* systems, although in the terminal affections, which are so frequently the immediate cause of death, the lungs and the brain are not infrequently involved.

*Digestive System.* Disorders of digestion and failure of appetite are common, but it is remarkable that, in the later stages, the appetite may be very good, and occasionally there is a craving for food of an unusual kind, for instance, a desire for meat in the case of natives, to whom it is forbidden by the laws of their caste. Intestinal disturbances are very common, and diarrhoea, of an extremely obstinate and intractable kind, is usually present at one or other stage of the disease. This is most frequent in the later stages, and plays no small part in the drain on the vital powers, which reduces the patient to such a pitiful state of exhaustion that he falls an easy victim to one of the complications referred to below. Blood is not infrequently found in the stools, and the symptoms may be those of dysentery, and due to an invasion of the gut by *Amoeba* or by the *Bacillus dysenteriae*, but it may also be due to an ulceration of the colon, which is apparently specific, since the "Leishman body" has been found in such ulcers by Sir P. Manson and Dr. Low, by Lieut. Christophers, and others. The intestinal symptoms may be further complicated by the presence of Entozoa, to which the *Assamese* are especially liable; *Intestinus duodenalis*, for instance, is so frequent in that country that Col. Giles, in his investigation into the nature of kala azar, was led to consider this parasite the cause of the disease.

Many other symptoms have been noticed in individual cases during the course of the disease, but it has been thought advisable to mention those only which, from the regularity of their appearance, are of common occurrence and therefore of diagnostic importance. Patients suffering

from a disease so chronic and exhausting as kala azar are peculiarly prone to intercurrent attacks of other bacterial or protozoan diseases, which may thus lead to great variations in the clinical picture. It is well to bear this in mind in diagnosing a case from the symptomatology alone, and in the absence of definite proof of the presence of the parasite.

*Terminations.*—Cases of kala azar tend, in the enormous majority of instances, to death. While this may occur at any stage of the disease, usually during an acute attack of pyrexia, it occurs more commonly at the end of the second stage or during the final stage of cachexia. The apparent cause may be simply asthenia or exhaustion, but, as a rule, sufferers succumb to some complication or terminal affection. The most frequent of these are diarrhoea, dysentery, cancrum oris, lung complications such as pneumonia, tuberculosis, or oedema, hæmorrhages from the stomach or bowel or into the membranes of the brain. Perforation of an intestinal ulcer may lead to a fatal peritonitis; meningitis and oedema of the glottis have been met with in a few instances.

*Mortality.*—Kala azar is one of the most fatal of tropical diseases; during the height of its ravages in Assam the death-rate was as high as 96 per cent, while, since then, it is said to range between that figure and 70 per cent. As far as evidence has been collected with regard to the endemic disease this form appears in no degree less fatal, although the average duration of the illness is said to be somewhat longer. The difficulties of recognising the disease in its earlier stages have already been mentioned, and it is quite possible that slight cases may occur, followed by recovery, which, if included, would lower the general death-rate; but it is at least certain that when once the disease is established the patient's recovery is extremely improbable, and that if he has entered upon the third stage, or during the second stage is attacked by some other grave disease, death is almost inevitable. In the case of Europeans, in whom the disease is by no means uncommon, the fatality is as high as in natives, and among those who have reached England, suffering from either form of the disease, I have neither seen nor heard of a recovery.

*Diagnosis.*—In the earlier stages there is nothing specially characteristic in the fever or other symptoms; and although the absence of malarial parasites and the resistance to quinine may arouse suspicion, there are undoubtedly other fevers of unknown causation in tropical countries which may increase the difficulties of early diagnosis. Later, the history of the case and the presence of the majority of the symptoms detailed above make up a clinical picture which is fairly distinctive, while the existence of previous cases in the patient's family or neighbourhood increases the probability that the case is one of kala azar. Greater difficulty may be found in the endemic form, especially in a district where the existence of the disease has not been suspected. I have recently received reports from Indian stations in which the finding of one case has led on investigation to the discovery of many more, the real nature of which had, till then, been unrecognised. The blood changes, and especially the leucopenia, are sufficiently constant and

be of special diagnostic value, while a history of transitory hemorrhages, and purpuric eruptions is rarely wanting. Kala is likely to be confused with the condition known as malarial cachexia, and this confusion has existed, and still exists, to so large an extent that a revision of the classical symptoms of malarial cachexia is necessary in the light of our knowledge of the existence of the disease of kala azar. The difficulties are not simplified by the fact that cases of kala azar may and do suffer from malaria, but even if the malaria, under appropriate treatment, will disappear, it does not bring about any improvement in the general condition. Certainty can, however, be obtained by means of splenic or hepatic puncture which will disclose the presence of the "Leishman body" in the tissue. But failure to find them should not necessarily be taken as evidence against kala azar, as they may be missed unless the tissue has been broken up by the needle-point and the parasites in this way escape from the cells into the blood which is withdrawn through the needle. Should blood only be withdrawn no parasites may be found, but subsequent examination after death may prove them to have been present. It must be remembered that the operation of splenic puncture is not absolutely free from danger, several cases of fatal hemorrhage having occurred; hepatic puncture presents fewer objections, and is as a whole preferable. In Europeans, the general appearance, the color of the skin, and the absence of malarial parasites are, I think, characteristic, and in the past led me to distinguish the endemic disease under the name of "Dum-Dum Fever," before finding that it was identical with kala azar in one of these cases at Netley (25).

5.—From what has been said as regards mortality it follows that the prognosis is extremely unfavourable. Still, recovery is not hopeless, and Major Rogers has reported cases in which, the presence of the disease in the spleen having been proved, subsequent exploration shewed that the parasites had disappeared coincidently with complete restoration of health. Generally, the later the stage of the disease the worse the prognosis. Prolonged diarrhoea or dysentery is of evil omen, as are also hemorrhages or oedemas, or the occurrence of any of the complications mentioned above. On the other hand, favourable signs are an absence of complications, long fever-free periods, and a moderate degree of leucocytosis. Major Rogers (50) lays stress on the prognostic value of the count of the white blood corpuscles, which, if totalling 2000 per c.mm.—and of these at least half should be polymorphonuclears—is a sign of amelioration and recovery.

6.—As may be gathered from the terrible mortality of kala azar, the treatment has been most unsatisfactory in the past, and at the present time the prospects of success are little if at all better. Innumerable cases have been tried and abandoned as useless, and it would appear that the prospects of prevention are better than those of cure. Still, recovery is not hopeless, and further research may put us in a position to imitate what nature appears able to effect in certain cases.

Quinine is the only drug whose value is still debated; Major Rogers (42) considers that, if given early, in large enough doses, and before the leucopenia has become extreme, it may do good, chiefly by controlling the fever and in lengthening the periods of apyrexia. On the other hand, it has been pushed *ad nauseum* by many who now regard it as absolutely valueless. In the presence of such a desperate disease and the absence of alternatives it should certainly be tried, if necessary by hypodermic injection; it is best employed during the apyrexial intervals, or when the temperature is below 101° F. Arsenic, iron, nux vomica, etc., are considered quite useless. Another line of treatment is to attempt to combat the leucopenia by the administration of red bone-marrow, either raw or in the form of tablets. This has the effect at times of increasing the number of polymorphonuclears, and if this can be effected benefit may follow; good results have been claimed for it, and, though it certainly fails in many cases, it is worthy of more extended trial.

Good nursing and a suitable regimen are of importance, great care being taken to avoid upsetting the digestion by an unsuitable diet. Diarrhoea may occur at any stage, and every effort should be made to control it by dieting and the use of astringents such as bismuth and salol; in the later stages it is most intractable, and may become a dangerously exhausting complication. The other complications demand their appropriate remedies or palliatives, but the extreme exhaustion caused by the systemic disease seriously handicaps the physician, and complications such as pneumonia, cancrum oris, frequently cause death.

Change of climate, or at least removal from the district in which the disease was contracted, has been advocated, and recovery in the case of natives has sometimes coincided with such change. I have not, however, seen or heard of a recovery in the case of Europeans returning to England; possibly, had the disease been earlier recognised, they might have benefited by the change.

*Prophylaxis.*—Much may be hoped from preventive measures when the complete life-history of the parasite is worked out, and the channels by which it enters and leaves its human host are recognised. Until we are in possession of this knowledge nothing can be done, at least in the endemic form of the disease. In the epidemic form good results are stated to have followed the segregation measures advocated by Major Rogers (45), although these were formulated at the time he considered the disease to be malaria. These measures, which aimed at the segregation of all cases as soon as recognised, together with their families, and the abandonment and destruction of the quarters in which they lived, have been successful in preventing the spread of the disease among coolies working in the tea gardens of Assam. Quinine has also been advocated as a prophylactic.

W. B. LEISHMAN.

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## MALARIA

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**SYNONYMS.**—Ague ; Paludism ; Intermittent Fever ; *Paludisme* (Fr.) ; *Wechselfieber* (Ger.) ; *Paludismo* (It.).

**Definition.**—A specific infectious disease, due to the invasion of the blood by several species of hæmosporidia of the genus *Plasmodium* malarie. This disease manifests itself, according to the species of infecting parasite, in three types which are distinguished in common by the occurrence of periodical, intermittent, or subintrant febrile paroxysms.

**Historical Note.**—Easily recognisable descriptions of the malarial fevers are to be found in the oldest medical writings, and remarkably

accurate accounts of many forms of the disease occur in the works of Hippocrates, Galen, and Celsus. By the older authors, however, no distinct separation was made of that group of fevers which we now know as malarial.

Three epochs may be recognised in the advance of our knowledge concerning malaria. The first of these began with the introduction of the use of cinchona in 1640, and the discovery of its specific action in a limited class of febrile diseases. With this period are especially associated the names of Sydenham, Torti, and Morton. The contributions to the literature by these authors and by their worthy successor Lancisi contain much that holds good to-day. The hypothesis of the parasitic origin of the disease was, indeed, adhered to by all of these authorities, and, in the light of our present knowledge, the accuracy of some of the older hypotheses is truly remarkable.<sup>1</sup>

But despite these clear-headed men, confusion still existed as to the proper application of the term malaria until the beginning of the second great epoch in 1880, with the discovery by Laveran of the specific cause of the disease.

The once prevailing conception of the manner of infection in malaria is reflected in the term by which it has come to be known—"mal' aria." But there were many other hypotheses. Amongst other time-honoured conceptions was that of the transmission of the disease by suctorial insects. King (1883), Laveran (1891), and Bignami (1896), suggested that the mosquito might be the infecting agent, while Sir P. Manson (1894) brought forward arguments in support of the conception that this insect might play the part of intermediate host of the malarial parasite. But doubt and uncertainty with regard to the manner of infection prevailed until the opening of the last epoch in the advance of our knowledge—the demonstration of the agency of the mosquito in the transmission of malaria (1897-99) by Prof. Ronald Ross, and the Italian school (Grassi, Bignami, and Bastianelli).

**Etiology.**—*Manner of Infection.*—The infectious agent of malaria—*Plasmodium malaria*—is introduced into the human organism by the bite of mosquitoes of the family Culicidæ, sub-family Anophelinæ, which have themselves become infected by biting individuals whose blood contained gametes of the malarial parasites.

<sup>1</sup> Especially striking is the observation of Rasori [1762-1827]. Calandruccio, *Agosto* *Bassi di Lodi, il fondatore della teoria parasitaria*, etc. Catania, 1892, 70. "For many years I have held the opinion that the intermittent fevers are produced by parasites which call forth a new paroxysm by the act of their reproduction which occurs at more or less rapid intervals according to the species." Alongside of such a remarkably accurate hypothesis it may be of interest to quote the curiously chosen words of Dr. Thomas Fuller, in the preface of his *Eranthematologia* (4<sup>th</sup>, London, Charles Rivington, 1730), resignedly saying: "I believe with all my Heart, that Nature doth Geometrize in all her Works, and constantly keepeth exact Proportion, Measure, and Number; but withal I am as much assured that we have not Capacities to take in a distinct Knowledge of them. . . . Can any Man, can the Men in the World, tho' assisted by Anatomy, Chymistry, and the best Glasses, pretend positively and certainly to tell us, what particles, how sized, figured, situated, mixed, moved, and how many of them are requisite to produce a quartan ague, and how they specifically differ from those of a tertian. . . ."



It is important at the outset of a consideration of this disease to realise that malaria does not appear spontaneously without the existence of certain definite conditions: (1) The presence of Anopheline. (2) The existence or recent presence of cases of malaria (relapses or infections acquired elsewhere) from which the mosquitoes may derive the infection. (3) Climatic conditions favouring the activity of the mosquito, suitable for its infection and for the further development of the oocysts of the parasite. (4) Susceptibility of the mosquito and of the individual bitten to infection. In the absence of any one of these factors an outbreak of malaria is impossible. Thus, there are many regions in which Anopheline are present without the existence of malaria, while again, localities which are definitely infected are quite safe at seasons of the year in which the climatic conditions are such that mosquitoes do not bite, or that the oocysts of the parasite are incapable of development. Moreover, it cannot yet be asserted that all Anopheline are capable of transferring the disease. While there is, at present, no evidence that other Culicidæ are capable of acting as hosts of *Plasmodium malariae*, it is known that *Culex pipiens* plays this part with regard to the closely allied parasites of birds. At the present time the following mosquitoes have been shown to be capable of transferring malarial infection. *Anopheles bifurcatus* (Europe); *A. maculipennis* (Europe and North America); *A. japonicus* (Japan); *A. marthæ*, *A. parsoni* (Cambodia); *A. vacanti* (Tonkin); *Muzonyia christophersi*, *M. ulurfacies* (India); *M. fuscata*, *M. superpecta*, *Myzomyia paludis* (West Africa); *M. constanti* (Madagascar and Reunion); *Paratophorus costalis* (Africa); *Nyssorhynchus latzi* (Brazil); *N. cubensis* (Panama). It is doubtless true that numerous other Anopheline transfer the disease. The brothers Sargent have recently found sporozoites, probably malarial, in the salivary glands of *A. algeriensis* and *Myzomyia hispaniola* in Algeria.

*Geographical Distribution.* Malarial fevers are widespread throughout the temperate and tropical regions of the world. The disease is rarely seen in cold climates; never above the latitude of 60° N. The severer types of infection are endemic in the tropics, the milder forms alone prevailing in temperate climates. Malaria is especially common in low, marshy regions, along the banks and deltas of large rivers and lakes.

In Europe the disease prevails in the lowlands about the coast of Italy, Sicily, Greece, Corsica, and Sardinia, and along many of the rivers, such as the Tiber and Po. Malaria is also met with about the coast of Spain, Portugal, and France. In the interior of France mild forms of intermittent fever are seen in Sologne, Brenne, Bresse, and Dombes, although cultivation and drainage are rapidly improving the conditions. The same is true of Belgium, the Baltic coast of Prussia, Silesia, and the plains of the rivers Rhine, Weser, Elbe, Oder, and Vistula. In Austria-Hungary the malady is common in Galicia, along the Adriatic coast and the valley of the Danube. Malaria prevails in many parts of the Balkan Peninsula and in Southern Russia, especially

along the Volga, about the borders of the Black and Caspian seas, and in the Transcaucasus.

In *Asia* malaria is widespread. It is common on the coasts of Asia Minor, Persia, and Arabia, in Turkestan, in Cochin China, Tonkin, throughout the south-east coast of China, and in Formosa; in the lowlands and along the banks of the great rivers in India, in Ceylon, in the Malay Peninsula, throughout the East Indies and in the Philippines. In Japan the disease is infrequent and mild.

*Australia* and most of the islands of Oceania are free from the disease.

In many parts of *Africa* the malarial fevers are especially prevalent. In the North they are observed in Egypt, in those regions which are periodically under water, in the lowlands of Abyssinia and Nubia, in Algeria, especially on the coast and about the rivers, as well as on the coast of Tripoli and in parts of Tunis. About the coast of tropical Africa, on the neighbouring islands and along the rivers, the most virulent forms of the disease are met with, especially upon the West coast from Senegal to Congo.

In *North America* malaria is observed along the eastern coast from New England to Florida. North of Maryland, however, the severer forms are rare. Mild intermittent fever is also met with in some low regions about the great lakes in the United States and in Canada. The disease is common in the valleys of the Mississippi and its tributaries. It occurs with great intensity in the lower Mississippi valley, especially in the delta and along the coast and the banks of the rivers of Louisiana and Texas. Mild forms of malaria prevail in the valleys and along the rivers of the Pacific coast. In the lowlands of *Mexico* and in *Central America* the severest forms of the disease are seen. The deadly Chagres fever of Panama is a form of æstivo-autumnal malaria. In the *Antilles* malaria occurs more or less extensively. In *South America* it is frequent about the coast, notably in Guiana, but also in the northern part of Brazil, in Bolivia, Paraguay, and Uruguay. In the Argentine Republic malaria is rare.

*Influence of Climate and Season.*—The climatic conditions under which malaria flourishes are those favourable to the development and activity of Anophelinæ, *i.e.* heat and moisture. In temperate climates the disease appears only during the warm season of the year<sup>1</sup>; while in the tropics, although occurring through much longer periods of time, it prevails especially in the wet season. In Rome the epidemic occurs in the latter six months of the year, the disease being most frequent in August and September. In Baltimore our figures agree closely with those of the

<sup>1</sup> What is known of the conditions under which the parasites develop in the stomach-wall of the mosquito clearly explains this. The oöcysts grow best at temperatures of from 20°-30° C. They are killed at temperatures steadily under 16° C. The infected mosquito may, however, be exposed for short periods to temperatures considerably lower than this—as low even, as from 10° to 13° C. for an hour—without complete destruction of the organisms, provided the subsequent conditions are favourable. If the temperature be under 16° C. the oöcysts are destroyed (Jancsó). Anophelinæ may bite at a season considerably earlier or later than that which is suitable for completion or the development of the oöcyst.

Italian observers, although the largest number of cases appears in September and October.

Season has also an influence upon the type of malaria. Although all forms of the disease are more frequent at the height of the malarial season, yet during the months of September and October the majority of the cases in Baltimore are infections with the æstivo-autumnal parasite, which, before the month of July, are extremely rare, the enormous majority of cases in the spring and early summer being due to the tertian organism.

The following table illustrates the seasonal variations in the prevalence of the individual types of malarial fever :

	Jan.	Feb.	Mar.	Apr.	May.	Jun.	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Total.
tertian	12	12	28	51	76	68	131	161	153	168	54	17	931
æstivo-autumnal	3	1	0	1	0	0	3	0	2	1	4	2	17
combined	5	1	2	5	2	3	37	99	191	203	63	22	633
	0	1	1	0	0	1	3	3	4	11	6	2	32
	20	15	31	57	78	72	174	263	350	383	127	43	1613

As the preceding table shews, the malarial epidemic in temperate climates disappears soon after the onset of cold weather and frosts. Most cases of the disease occurring in the first half year are relapses. The rare instances of apparently primary malaria observed in the spring are in great part, probably, examples of a prolonged period of incubation, cases in which the symptoms of the primary attack were so slight as to be overlooked. In Baltimore, as in Rome, the epidemic of infections with the tertian parasite begins in the early summer. The epidemic of infections with the æstivo-autumnal parasite is, properly speaking, an æstivo-autumnal phenomenon. The few instances of infection with the tertian parasite occur in the autumn.

The valuable observations accumulated by the Italian Society for the Study of Malaria have demonstrated that the epidemic of primary attacks almost invariably preceded, for a greater or less period of time, by the epidemic of relapses—just as might be expected from what we know of the manner of infection.

*Influence of Moisture.*—Moisture plays a very important part in the prevalence of malaria. The most malarious regions are low and marshy, situated about rivers or lakes. In the tropics the rainy season and the period immediately succeeding it are especially dangerous. Moisture is necessary for the development of the eggs and larvæ of Anophelinae.

*Soil.*—The most dangerous localities are those with an impervious subsoil, where pools and collections of standing water are common.

Swampy districts, where the surface of the ground is covered for a part of the time by water, are especially favourable for the development of Anophelinæ and malaria. For many years it has been known that proper drainage and canalisation of such areas are followed by great improvement in the hygienic conditions with regard to the malarial fevers. Lutz has shewn that in some wooded and mountainous regions, where there is no standing water, larvæ of Anophelinæ may develop in great numbers in fluid collected and secreted between the leaves and in the folds of certain plants. Epidemics of malaria may break out in such localities.

*Altitude.*—Malaria is rare at high altitudes. The disease has, however, been observed in Italy, and in South America at elevations of nearly 10,000 feet. Consideration, however, of our knowledge of the habits of Anophelinæ, would lead to the anticipation that, with suitable telluric and climatic conditions, altitude *per se* would play but a small part. The reported existence of malaria in localities which, from general geographical conditions, might be expected to be free from the disease should always be carefully investigated, for relapses may occur in any climate and under a great variety of conditions.<sup>1</sup>

*Drinking-Water.*—The popular idea that malarial fever depends often upon the character of the drinking-water is based largely on errors in diagnosis. Investigation usually proves that the condition regarded as malarial is in reality enteric fever. There is no evidence that the character of the drinking-water has any influence whatever upon the development of malaria.

*Influence of the Time of Day on the Liability to Infection.*—It has long been known that the dangers of malarial infection are greater during the evening and at night than by day. Anophelinæ are for the most part night-biting mosquitoes.

*Influence of Age and Sex.*—Children and infants are more susceptible to malarial infection than adults. This is, probably, in part, because their thin and delicate skin renders them peculiarly subject to mosquito bites. Some years ago I was told of a young woman who always slept with her baby sister in order to escape the mosquitoes which usually attacked the infant by preference. Koch, who first pointed out the frequency of malarial infections in the early years of life among the natives of the tropics, regards the prevalence of the disease among the children of a given locality as an index of the extent to which malaria exists in that region. Apart from this, age and sex have, apparently, no bearing upon the prevalence of the disease except in so far as they affect the liability of the individual to exposure.

*Race.*—In general the dark-skinned races, who have for generations inhabited malarious regions in the tropics, appear to possess a relative immunity to the disease. This may, however, be in part acquired as a

<sup>1</sup> I have mentioned elsewhere (11) an instance of a relapse of tertian fever occurring during a walking trip in a most healthy region of the Alps, nearly eighteen months after the last paroxysm.

result of the frequent infections in youth. Koch's observations in Africa, as well as those of the Italian school, support this interpretation. On the other hand, it is undoubtedly true that in the United States the negroes who have inhabited the country for many generations, living under conditions not essentially different from those of the neighbouring whites, are much less liable to malarial infection. Our observations in Baltimore shew that the susceptibility of the negro is only about a third that of the white. It may be that the thick skin of the African renders him somewhat less susceptible to the bites of mosquitoes.

*Occupation*—The influence of occupation on the frequency of malaria depends wholly upon whether the individual is obliged to expose himself to infection during dangerous seasons of the year and at dangerous times of the day. In the rice fields of the southern states of America, the disease prevails among those who are obliged to spend their evenings and nights on the plantation, while it is rare among members of the same family who pass their time, during the dangerous seasons of the year, in the sandy "pine lands" often but a few miles distant. Those who live in well screened houses are in little danger, while individuals sleeping in huts or unscreened dwellings are especially prone to infection.

*Influence of Population and Settlements on the Prevalence of Malaria*

Uninhabited regions, although infested by *Anopheles* are free from danger. Infected mosquitoes occur only in the immediate neighbourhood of settlements of infected individuals. It has often been observed that the members of exploring expeditions have been free from the disease as long as they have been in regions remote from native or white settlements.

*Cycles of Severity*.—Remarkable and hitherto inexplicable variations in the prevalence of malaria in districts in which it is endemic have long been recognised. In some regions the disease may, indeed, almost or entirely subside, to appear again after a period of years.

*Congenital malaria*.—The possibility of the transmission of the parasite through the placental circulation has, for years, been a disputed point. It was generally accepted by the older observers, and such a case at that of Buchek, in which a child born of a malarious mother and dying three hours after birth, shewed a large pigmented spleen together with pigment in the portal vein, is most suggestive. Since the discovery of the parasite the presence of organisms in the blood of the new born child has been reported in several instances, notably those of Bein, Bouzian, and Peters, but in all of these cases a sufficient length of time had elapsed since birth to allow of a fresh infection. On the other hand, in a number of recorded cases, the blood of infants born of malarious mothers, as well as the placental blood, has been examined by observers who have made a special study of this disease (Bignami, Bastianelli, Caccini, Thayer, Schaudinn). In none of these was there evidence of infection of the child, although parasites were found in the peripheral blood of the parent and once in the maternal placenta. Hille described malarial parasites in the blood of the umbilical cord in two cases; the article, however,

seems to me unconvincing. The transmission of malaria from parent to offspring is, at all events, a rare occurrence.

**Immunity.**—There is evidence of the existence of a certain degree of immunity, both natural and acquired, against the disease. The existence of a natural immunity is suggested; (1) by the relative insusceptibility of some dark races; (2) by the exemption from disease of certain individuals who live in most malarious districts and are constantly exposed to infection; (3) by the insusceptibility of occasional subjects to experimental inoculation of malarial blood. Generally speaking, one attack of malaria does not protect against subsequent infections; there is, however, some reason to believe that severe and repeated attacks do, in some instances, result in a partial or complete immunity of doubtful duration. Cases of this sort have been described by Celli, and can be observed in all severely malarious districts, while Koch, as has been said, regards the relative immunity of the dark-skinned races as largely due to the great frequency of infections during childhood. The remarkable waves of intensity of malarial epidemics in localities in which the disease is endemic, may, as Celli suggests, be due to the periodical development and exhaustion of a certain degree of immunity among the population.

**Pathological Anatomy.**—Death so rarely occurs in the milder forms of acute malaria that descriptions of the pathological changes are based almost entirely upon appearances observed in cases of pernicious fever of the æstivo-autumnal type. The most striking point in the appearance of all the organs is the general slaty-grey colour, due to the accumulation of pigment produced by the parasites. This pigmentation is more extensive in older infections, and may vary considerably in its localisation as is true also of the parasites themselves. This is in part because much of the pigment is contained within parasites, the irregular distribution of which in the internal organs is one of the most remarkable features of malarial infections. While found to a greater or less extent in the general circulation, the parasites are nearly always present in special abundance in certain organs, notably the spleen and bone-marrow. In many pernicious cases, however, individual organs may be the seat of a peculiarly intense infection, and this special localisation of the infection may and often does result, not only in grave local disturbances of function, but also in definite anatomical changes in the affected organ. Cases in which individual organs are thus, as it were, picked out often present distinctive clinical phenomena, traceable to the disturbances of function of the affected part; these special symptoms may dominate the clinical picture.

In mild cases the *brain* shews few changes. The grey cortex is as a rule of a deepened, somewhat chocolate colour which may be striking. Areas of punctiform hæmorrhages may be found. In severe cases the capillaries are crowded with pigment-bearing cells and parasitiferous corpuscles, so much so, indeed, as to form a complete injection. The endothelium of the capillaries is swollen and phagocytic, containing



parasites, pigment, and often degenerated and infected red corpuscles. Thrombosis with these elements—the so-called “pigment thromboses”—with resultant hæmorrhage may occur. These hæmorrhages, usually of focal distribution, may be sufficiently extensive not only to cause acute manifestations, but to result in secondary sclerotic changes (Spiller). Monti and Ewing have described degenerative changes in cortical ganglion cells, changes due, doubtless, in part to circulatory disturbances although, according to the latter observer, “the comparative uniformity of the lesions noted indicates that a general toxæmia is, even in cerebral cases, the more important causal element.”

The *thoracic organs* shew, as a rule, little that is characteristic beyond the occurrence of pigment bearing phagocytes in the capillaries. In a case in which cardiac failure was a striking feature, Ewing found large numbers of young parasites and pigmented cells completely filling distended capillaries throughout the heart wall. Similar observations have been made by Benvenuti.

The *spleen* is enlarged, and in acute cases, as in one studied by Barker, soft and almost diffuent. It is usually of a dark cyanotic colour due to pigment, and, in old cases, may be almost black. The enlargement may be so great as to result in rupture, either spontaneous or after slight injuries; thus, I know of an instance of rupture following aspiration for diagnosis. The pulp is crowded with red blood-corpuscles containing parasites which are usually in the later stages of development—bodies with central pigment clumps or blocks and segmenting bodies. Younger forms are relatively uncommon. There are great numbers of phagocytes, usually mononuclear elements, some of which are about the size of the mononuclear leucocyte of the blood, some macrophages laden with pigment, parasites, infected or degenerated red blood corpuscles, and, sometimes, smaller phagocytes. Focal necroses of the pulp are not uncommon. Chronic or frequently repeated infections result in more or less characteristic changes in the spleen which may become greatly enlarged. On section, the surface is of a somewhat slaty colour, the trabeculae are very prominent; the reticulum, vascular sheaths, and septa are thickened, while single or multiple lymphatic cysts may arise. The gradual evolution of these changes has been minutely described by Bigami. Amyloid change has been observed after long and chronic infections.

The *liver* is usually enlarged and of a dark brown, or, if the infection be severe, of a slaty-grey colour. There is always marked cloudy swelling. The capillaries are dilated, and contain numerous pigment bearing phagocytes, large macrophages being commonly present. The endothelium of the capillaries is often phagocytic. The number of parasites and phagocytes in the liver varies greatly in different cases and in different parts of the organ, although, as a rule, the vessels contain few intra-corpuscular parasites. Pigment bearing cells are often found in the perivascular tissue of the portal spaces, while the liver cells themselves may contain pigment and altered red blood corpuscles. Disseminated areas of



focal necrosis, associated with capillary thromboses, may occur (Guarnieri, Barker); the necroses may be so large as to be recognisable by the naked eye. With frequently repeated infections the liver may undergo changes resulting in enlargement with the development of more or less well-marked perilobular fibrosis, which has, however, little tendency to contract; there is considerable irregularity in the size of the lobules, and more or less capillary dilatation. As in the case of the spleen, these progressive changes have been ably described by Bignami. Amyloid change may occur after long-continued and repeated infections. There is no satisfactory anatomical evidence that malaria alone is a cause of portal cirrhosis of the liver.

*Kidneys.*—The renal changes in malaria are usually slight as compared with those in the liver and spleen. The kidneys may be slightly enlarged, the cortex rather pale, the markings a little indistinct. There is usually little or no evidence of pigmentation. Microscopically, infected red corpuscles and pigment-bearing leucocytes are often found in moderate numbers in the glomeruli and intertubular vessels. In some instances more severe changes may be found—degeneration and exfoliation of the capsular epithelium with albuminous exudates into the glomeruli and focal necroses in the cortex, especially in the area of the convoluted tubules. These changes, as may be readily seen, cannot be correlated with the insignificant number of parasites which are present, and are probably dependent upon circulating toxic substances. Ewing (103) has described a remarkable case of fatal acute hæmorrhagic nephritis in æstivo-autumnal malaria. In this instance the cortex was remarkably light in colour, while the medulla and papillæ were extremely dark and slightly rusty. The cortical markings were completely obscured, and there was widespread degeneration of the epithelium. The glomeruli contained a moderate number of pigmented cells and a few parasites, while the cavities of Bowman's capsules were distended by a granular coagulum. Most of the cortical capillaries were quite obstructed by the pressure of the distended tubules. The capillaries in the medulla and papillæ were crammed with infected cells and parasites, while the discharging tubules were filled with casts, sometimes entangling infected red blood-corpuscles and pigmented leucocytes. There was a large superficial infarction from occlusion of vessels by thrombi of infected red blood-corpuscles, and numerous miliary hæmorrhages from rupture of capillaries crowded with infected globules. In this instance the lesions produced by the special localisation of the parasites in the kidney dominated the clinical picture, and brought about the death of the patient. The grave changes occurring in hæmoglobinuric fever are discussed elsewhere (*vide*, p. 296). Amyloid change has been described in very chronic infections.

The changes in the *gastro-intestinal tract* are usually insignificant, consisting of a slight degree of melanosis. In other cases, however, the main localisation of the infection appears to be in the intestine. Here there is great injection of the mucosa with hæmorrhages and superficial necrosis and ulceration. The vessels are loaded with infected corpuscles and

igment-bearing cells, with resultant thrombosis, necrosis, and hæmorrhage. Such cases may present symptoms like cholera. Amyloid change has been observed after chronic infections. Pensuti has reported a remarkable case of chronic malaria with amyloid change in association with widespread atrophy of the intestinal mucosa. Inasmuch, however, as the case is unique, its dependence upon malaria cannot be definitely asserted.

The *bone-marrow* is often extensively pigmented. The small vessels contain great numbers of parasitiferous corpuscles and numerous macrophages. After frequently repeated infections there are usually signs of active hyperplasia, the marrow of the long bones becoming red in considerable areas. The degenerations which sometimes occur during acute infections may, however, result in considerable injury to the blood-forming function. A megaloblastic type of marrow, associated with changes in the blood characteristic of pernicious anæmia, has been described by Bignami and Ewing. There may be a complete lack of hyperplasia, resulting in fatal aplastic anæmia.

*Suprarenals.*—Barker has described pronounced changes in the suprarenals, *i.e.* irregular areas of vascular dilatation with numerous parasites in the distended vessels. Macrophages may be present in varying numbers, while the endothelium of the capillaries, as well as the true adrenal cells, are phagocytic. The other organs shew little that is characteristic.

**Clinical Description.**—The malarial fevers fall into three main types, according to the species of parasite causing the infection:—

- (1) *Tertian fever* (*Plasmodium vivax*).
- (2) *Quartan fever* (*Plasmodium malarix*).
- (3) *Æstivo-autumnal fever* (*Plasmodium falciparum*).<sup>1</sup>

The first two varieties, tertian and quartan, are sometimes classed as *regularly intermittent fevers*, in contradistinction to *æstivo-autumnal fever*, manifestations of which are considerably more variable.

Our knowledge of the period of *incubation* in malaria is based upon results of experimental inoculations by the bites of infected mosquitoes (Grassi, Bastianelli, Bignami, P. T. Manson, Jancsó), and on the observation of cases developing under close medical supervision, where the time of inoculation could be determined with comparative accuracy (Mariotti, Richi, Jackson). The interval between the time of invasion and the first febrile symptoms varies somewhat according to the type of infection.

In quartan fever the period of incubation is about 3 weeks; in tertian fever it averages about 14 days; in æstivo-autumnal fever, from 10 to 12 days. But the period of incubation may be much prolonged. Experimental inoculations have shewn that it varies inversely as the number of parasites introduced, while the physical condition, race, natural or acquired resistance, and general surroundings of the patient, as well as

<sup>1</sup> The malarial parasites are described on p. 74. In the nomenclature of the Royal College of Physicians of London the parasite of æstivo-autumnal fever is described as *Plasmodium falciparum* Grassi.—EDITOR.

the virulence of the parasite itself, must obviously play a part in determining the rapidity of the development of the symptoms. Celli has demonstrated experimentally an incubation-period of 47 days in quartan fever, while in another instance, in which the patient was treated before inoculation with phenocoll, the interval between infection and the onset of symptoms was 66 days. A possible explanation of the apparently prolonged periods of incubation in some cases is that, after spontaneous recovery from an infection the symptoms of which have been so mild as to have passed unrecognised, a relapse has simulated a primary attack.

**Symptoms**—1. **TERTIAN FEVER**.—Infection with the tertian parasite is the commonest form of malaria in temperate climates. The symptoms vary according to the presence of one or more groups of organisms.

(a) *Single Tertian Infections (Tertian Fever)*.—Infections with a single group of tertian parasites are characterised by intermittent febrile paroxysms, occurring at intervals approximately forty-eight hours apart, each paroxysm following closely upon the segmentation of the infecting group of organisms. *Prodromes* are slight. Two or perhaps four days before the initial attack the patient may complain of slight indefinite symptoms—headache, backache, anorexia, pains in the limbs, symptoms such as are common in any acute infection, though, often, the first seizure may come, as it were, entirely unheralded. The paroxysm is divided into three characteristic stages—the *cold stage*, the *hot stage*, and the *defervescence or sweating stage*.

The *cold stage* is immediately preceded by indefinite feelings of malaise, headache, and general lassitude, often by vertigo, and sometimes by nausea and vomiting. By this time a slight rise in the bodily temperature has already set in. Chilly sensations, at first interrupted by slight flushes of heat, soon follow, increasing until the patient falls into a general rigor. The chill may be very severe. The sufferer shakes from head to foot, and begs for coverings and hot applications; the teeth chatter; the movements are so violent that the bed may shake; the face is drawn and pinched; the extremities cold and shrunken; the skin is cool and often rather cyanotic; sometimes pale and moist. The pupils are usually dilated; the pulse small, rapid, and of rather high tension, sometimes irregular. Nausea and vomiting are common during the paroxysm, and there may be diarrhoea. The urine is increased in quantity. There is severe headache, and aching pains in the back and legs; sometimes vertigo and tinnitus aurium. The duration of the chill varies from ten minutes to an hour. Not infrequently no actual shaking may occur, the patient complaining only of chilliness. Occasionally sensations of cold may be entirely absent. Out of 332 cases of tertian fever occurring at the Johns Hopkins Hospital, chills or chilly sensations were present in 97.5 per cent. During the chill the temperature rapidly rises, reaching its maximum, as a rule, within two hours after the onset of the paroxysm.

With the subsidence of the chill, intermittent flushes of heat usher in the so-called *hot stage* of the paroxysm. There is a subjective sensation

of intense heat; the skin is flushed, hot, and dry; the conjunctivæ injected. The pulse remains rapid, but is softer and not infrequently dicrotic. The patient complains bitterly of headache, vertigo, pains in the back and extremities, and often of tinnitus aurium; he is very restless, and frequently delirious, tossing about and throwing aside the bed-clothes. (One of our cases, a patient with tertian fever, sprang out of the window in his delirium. But the patient may be dull and apathetic, complaining of severe headache and backache, and presenting an appearance not unlike that in enteric fever. Somnolence, and even coma, though very rare in this type of malaria, may occur. There is intense thirst. There may be a slight cough, while nausea, vomiting, and diarrhœa are common. Abdominal pain, sometimes referred to the region of the spleen, is not unusual. There may be bleeding from the nose. In children, convulsions of varying severity not infrequently take the place of the malarial paroxysm. The patient's appearance is characteristic; he is usually flushed, the conjunctivæ suffused and injected, the tongue dry and coated. The sallow, earthy hue of the skin, associated with a slight yellowish tint, is remarkably characteristic of the disease. If many paroxysms have occurred there is usually a slight anæmia. Herpes about the lips and nose is common. There is often slight bronchitis. The spleen is enlarged and usually palpable; soft in early cases; harder in those of long duration; after repeated attacks it may attain a considerable size, extending to or even below the umbilicus. Splenic enlargement is especially notable in children. Erythema or urticaria, sometimes of a remarkable morbilliform character, not infrequently accompanies the paroxysm. A purpuric rash is sometimes observed. Erythema nodosum has been described (Moncorvo, Riva-Rocci). During the hot stage the temperature reaches its maximum, which is often above 105° F. The duration of this stage is usually four or five hours, though it may be considerably longer.

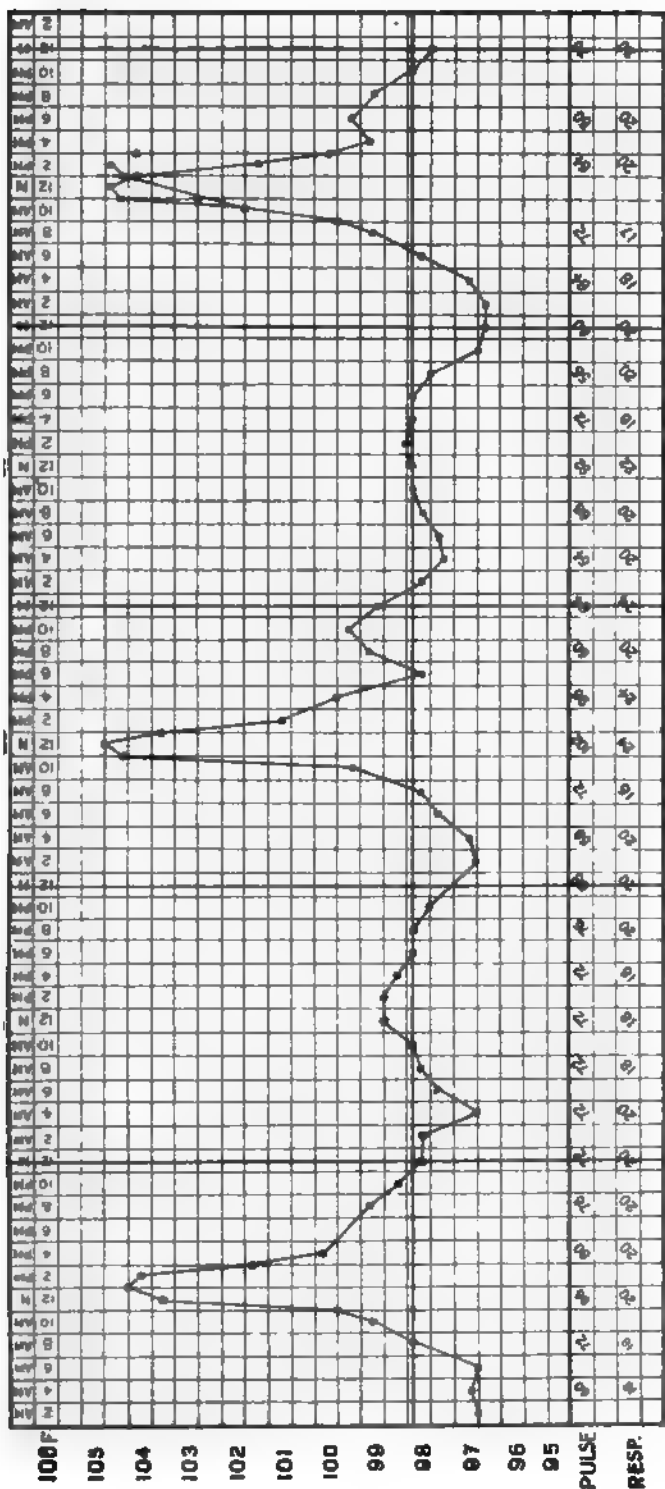
The onset of the *sweating stage* brings relief from the sensation of heat. The sweating soon becomes profuse, and sometimes drenching. The temperature falls rapidly, the pulse becoming slow and regular, while the patient often sinks into a refreshing sleep. Within a few hours, rarely more than four, the temperature falls below normal, usually remaining subnormal during the greater part of the intermission. The length of the entire febrile paroxysm in cases of single tertian malaria averaged, in our cases, about eleven hours. These paroxysms are more frequent during the day than at night, the onset occurring generally in the late morning hours.

During the greater part of the intermission, which lasts, as a rule, fully thirty-seven hours, the temperature is subnormal. The patient feels remarkably well—often, indeed, the effects of the paroxysm have entirely disappeared—and gets up and goes about his business, believing that he has recovered. But almost exactly forty-eight hours from the onset of the first paroxysm a second similar attack occurs, and, if treatment be neglected, febrile periods and intermissions alternate with great regularity. Although, as is well known, the cycle of existence of the tertian parasite

is about forty-eight hours, yet the periods of sporulation often occur at intervals slightly shorter or longer than this time. In such instances the resultant paroxysms appear at intervals somewhat less or somewhat more than forty-eight hours—so-called “anticipating” or “retarding” attacks. Retardation is sometimes observed in connexion with spontaneous recovery or after taking quinine.

Examination of the *blood* reveals the presence of one generation of tertian parasites. The first intracellular forms of the schizont become evident during the paroxysm. These are extremely delicate, pale, hyaline discs about  $1.5-3\mu$  in diameter. They are actively amœboid. Soon after the beginning of development fine, brownish pigment-granules appear, and increase in number with the growth of the parasite. On the day of intermission the young schizont has, at rest, a diameter of more than half that of the normal red blood-corpuscle. But the organism is rarely at rest; its amœboid activity throws it generally into irregular and bizarre shapes. The index of refraction of the parasite differs so slightly from that of the containing corpuscle that the outline of the body is often barely distinguishable, while the pigment-granules, collecting as they do, at the bulbous extremities of several pseudopodia, give the impression at first glance of three or four separate parasites, instead of a single irregularly-shaped organism. The surrounding corpuscle at this stage is already materially larger than its neighbours, and is, moreover, less decolourised. In some cases the decolourised corpuscle shews a number of glistening granules which, in specimens stained by Romanovsky's method, take a deep red colour—the so-called Schüffner's granules. On the day of the paroxysm, five or six hours before its onset, the parasites are nearly as large as the normal red corpuscle, and wholly immobile; the pigment is coarser, darker, and less active, and the surrounding corpuscle wholly decolourised and scarcely discernible. Shortly after this, beginning several hours before the paroxysm, early segmenting forms are seen. The pigment collects at one point in the organism, which assumes a somewhat granular appearance; glistening dots representing the chromatin of the individual segments begin to appear, and finally the outlines of the 12-24 separate merozoites become distinct. Segmenting bodies may be seen throughout much of the paroxysm. Large vacuolating and fragmenting bodies are also common at this period. After several paroxysms the large, non-motile, spherical gametes with actively dancing pigment-granules may be seen in varying numbers, and if the specimen be studied for over ten minutes, flagellation of microgametocytes may be observed with the liberation of microgametes.

The parasites are less abundant in the peripheral circulation during the period immediately preceding, and at the time of the paroxysm, than they are during the periods of intermission, because the mature bodies tend to accumulate in the internal organs, especially in the spleen. The onset of a paroxysm may be predicted with certainty from the discovery of segmenting bodies in the circulation. During the paroxysms, and to a certain extent at other periods of the infection, evidences of phago-







cytosis may be found in the presence of pigmented white elements, sometimes polymorphonuclear, often mononuclear in character, containing granules or blocks of pigment similar to those seen in segmenting forms. On a slide of fresh blood active phagocytosis may be observed at any stage of development of the parasite, whenever an organism breaks out of a red cell. The elements taking part in the phagocytosis observed in the fresh specimen are polymorphonuclear leucocytes; those containing the pigment blocks are usually mononuclear elements.

Further examination of the blood reveals a slight anaemia, if there have been several paroxysms. The leucocytes are reduced in number, the percentage of polymorphonuclear neutrophils decreased, that of the large mononuclear elements augmented. The *urine* in tertian fever shews no especially characteristic changes. A slight trace of albumin is often present, having been found in 38.3 per cent of 344 cases.

(b) *Double Tertian Infections (Quotidian Fever).* Infections with two groups of tertian parasites are commoner than single tertian infections. In these instances segmentation of a generation of parasites occurs daily, resulting in quotidian intermittent fever. Though the time of segmentation of the groups of parasites reaching maturity on successive days is often nearly the same, yet an analysis of the temperature chart usually shews a definite relation between the hours of onset and the character of the paroxysms occurring every other day. The symptoms differ in no essential from those in single tertian infections. The paroxysms are, however, somewhat shorter, lasting on an average between ten and eleven hours. The dependence of the symptoms upon two groups of parasites may sometimes be demonstrated by the administration of a small dose of quinine at about the time of a paroxysm. The drug, exercising its most active influence upon the extracellular organisms, segmenting bodies, and free merozoites, may, if administered at this time, by destroying the segmenting group of parasites, change the type of fever from quotidian to tertian. Examination of the *blood* shews two groups of tertian organisms at different stages of development corresponding to the time of onset of the paroxysms. Thus, at the time of a paroxysm, while one group is represented by full-grown parasites, segmenting forms and fresh hyaline bodies, the second generation, is present in the shape of half grown, pigmented, ameboid, intracellular elements.

(c) *Multiple Tertian Infections (Irregular Benignant Fever).*—Occasionally infections with multiple groups of tertian parasites may occur. In such cases the paroxysms, becoming subintrant, result in apparently irregular remittent fever. The diagnosis may be made by examination of the *blood*. Occasionally in severe multiple infections but few parasites are to be found in the peripheral circulation, the greater part of the development going on in the internal organs. Such cases, however, are unusual and exceptional.

2 QUARTIAN FEVER.—Infections with the quartan parasite are almost everywhere rarer than tertian malaria. In some localities they

are not observed. In Italy there are certain regions where quartan fever is especially frequent. In Baltimore, out of 1613 cases of malaria, there were but 17 instances of quartan infection.

(a) *Single Quartan Infections (Quartan Fever).*—In infections with a single group of quartan parasites the paroxysms, corresponding with the segmentation of parasites, occur with great regularity at intervals of approximately seventy-two hours. The paroxysms differ in no way from those of tertian fever, the periods of intermission—associated likewise with subnormal temperature—are, however, twenty-four hours longer. Slight anticipation or retardation may occur as in tertian fever. The diagnosis is readily made by the examination of the *blood*, which shews a single group of quartan parasites. Fresh young schizonts begin to appear in the red blood-corpuscles, as in tertian fever, during the paroxysm. A few hours later pigment-granules appear at the periphery of the parasite, the amœboid movements of which are much less active than in the tertian organisms. On the second day the schizont is somewhat larger, very slightly amœboid, the pigment lying at the periphery. The organism is at this stage easily distinguishable from the *Plasmodium vivax* by its relative lack of amœboid activity, its greater refractiveness, and the slight motility and peripheral arrangement of the pigment-granules. The surrounding red corpuscle is often rather smaller than its neighbours; it may already be of a somewhat deeper colour. On the third day the parasite is a little larger, and often of a somewhat ovoid shape; it is quite motionless. The pigment is coarse and peripherally arranged. The infected corpuscle is represented by a small rim of rather greenish or brassy-coloured refractive protoplasm. The whole body is smaller than the normal red blood-corpuscle. On the day of the paroxysm, sometimes as much as eight to ten hours before its onset, evidences of segmentation are observable. The small rim of surrounding corpuscle is barely visible, while the pigment begins to collect towards the centre of the parasite, flowing in in radiating lines. This is rapidly followed by the development of the characteristic regular segmenting bodies with six to twelve merozoites. Large vacuolating and fragmenting forms, as well as evidence of phagocytosis, are especially common at this period, as in tertian fever. Large pigmented, sexually-mature forms (gametes) and flagellate bodies may be observed at any time in older infections. Gametes are, however, less frequent in quartan than in tertian fever. Segmenting bodies begin to appear eight or ten hours before the onset of the paroxysm. The quartan parasites, occurring with much greater relative frequency in the peripheral circulation than either of the other species of malarial organism, are to be found in the fresh specimen of blood in even very mild infections. The discovery of segmenting organisms in the peripheral circulation in tertian fever is an almost certain indication of an impending paroxysm. In quartan fever, however, all stages of the organism may be studied in the blood in infections so mild as to be wholly free from fever.

(b) *Double Quartan Infections.*—In infections with two groups of



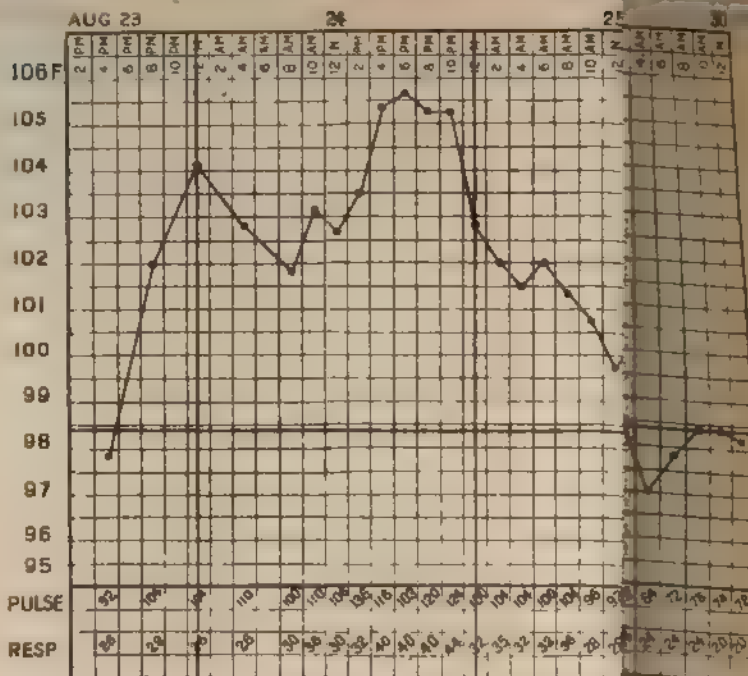
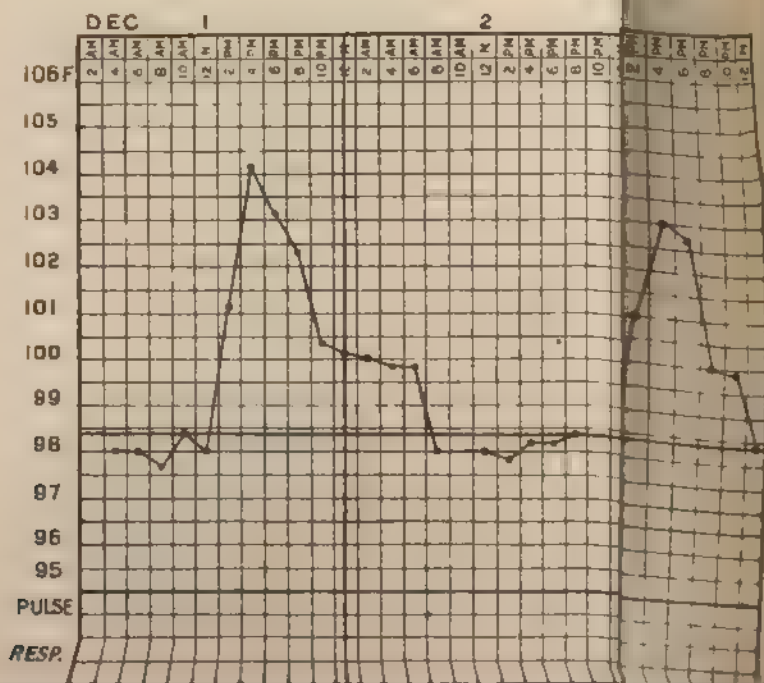


Chart 2



parasite, paroxysms occur on two successive days, followed by a period of intermission. The paroxysms are in every way similar to those in single quartan infection. The diagnosis is easily made by examination of the blood.

*Triple Quartan Infections (Quotidian Fever)*—Triple quartan infection results in quotidian intermittent paroxysms, which may resemble in every way double tertian fever. A careful study of the chart will generally, however, reveal a similarity between the hours of onset and character of the paroxysms, occurring seventy-two hours apart, sufficient to indicate the nature of the infection. Examination of the blood reveals the presence of three groups of quartan parasites. Since, as mentioned above, quartan organisms are so common in the peripheral circulation, it is often the case that single or double quartan fever may occur in a patient whose blood shows three distinct groups of parasites, only one or two of which have reached a degree of development sufficient to cause a definite febrile reaction. The urine in quartan fever shows no characteristic changes. A trace of albumin is often present.

3. *ÆSTIVO-AUTUMNAL INFECTIONS (Æstivo-autumnal Fever)*. The æstivo-autumnal fevers prevail in the tropics, occurring in temperate climates only at the height of the malarial season. Infections with *Plasmodium falciparum* (*Laverania malarie*) are especially notable for their tendency toward irregularity, and toward the development of remittent or subcontinuous fever, as well as for the frequency with which "pernicious" symptoms appear. The continued and remittent character of the fever in many cases depends probably on the arrangement of the parasites in groups, the segmentation of which extends over long periods of time, resulting in paroxysms of longer duration, which, from their special tendency to anticipation and retardation, often become subintant. Again, infections with multiple groups of parasites are frequent. In most cases definite paroxysms may be easily traced upon the carefully kept clinical chart, and on analysis the febrile curve is more or less regular. Inasmuch as the cycle of development of the common variety of æstivo-autumnal parasite lasts about forty-eight hours, the intermittent fever of a stivo-autumnal malaria is of the tertian type—a fever which has fairly definite characteristics (*malignant tertian fever*). The striking feature of æstivo-autumnal fever is the great length of the paroxysms, which are often of over twenty-four hours' duration, differing materially from those of the regularly intermittent fevers. The onset may be abrupt, but is frequently gradual and insidious. The chill was absent in nearly one-third of our cases, and, when present, was often abortive or delayed, coming on only after the paroxysm was well underway. The general symptoms are usually severe, the gravity of these so-called "dumb chills" being well recognised by the inhabitants of malarious districts. There is severe headache, intense aching pains in the back and extremities, often vertigo and tinnitus aurium; nausea, vomiting, and diarrhoea, especially in children, are frequent. Delirium, mild and muttering, or in some pernicious cases violent and maniacal,

is common. In other instances the dull, drowsy, apathetic condition suggests enteric fever. The same cutaneous manifestations may be observed here, as in the regular intermittents. During the fastigium of the paroxysm there may be considerable oscillations and variations in the temperature curve. Marchiafava and Bignami have described as characteristic a pseudo-critical fall in temperature, followed by a pre-critical rise; this we have often seen. The defervescence is more gradual, and the sweating stage less distinctive and characteristic than in tertian and quartan fever. Paroxysms may occur at intervals considerably greater or less than forty-eight hours. Thus, I have observed an instance of æstivo-autumnal fever, with paroxysms recurring with considerable regularity, at intervals of as much as fifty-six hours, as well as cases with paroxysms every thirty-eight hours. The pseudo-critical depression may be so marked as to give rise to a complete intermission, resulting in a complicated clinical picture. Infections with two groups of parasites, causing quotidian or continued fever, are very common.

Although, like many others who have worked at malaria, I have been unable to distinguish among the æstivo-autumnal parasites any definite morphological differences justifying a division into distinct varieties or species, it must be acknowledged that the observations of Bignami and Bastianelli, Mannaberg, Craig, Caccini, and others, appear to shew that occasionally cases of æstivo-autumnal fever occur with quotidian paroxysms, due to infection with a single group of parasites whose cycle of existence is limited to approximately twenty-four hours. The paroxysms differ from those already described only in being, as a rule, rather shorter than those due to parasites with a longer cycle of development. Cases of irregularity, due to prolongation, anticipation, or retardation of the paroxysms, with resultant subcontinuous or remittent fevers are common. The average length of the æstivo-autumnal paroxysm in our cases was between twenty and twenty-one hours.

*Irregular Fevers.*—Anticipation or retardation of the paroxysms, excessive oscillations in the temperature curve during the febrile period, as well as highly developed pseudo-crises, often result in a very irregular temperature curve. The irregularity may be so great that careful study of the chart fails to reveal the fundamental type of the infection.

*Remittent or Subcontinuous Fevers.*—As a result of prolongation, anticipation, or infection with multiple groups of parasites, the paroxysms not infrequently become subintra, with consequent remittent or continued fever. The absence of the chill, the dull, drowsy, typhoid condition, the muttering delirium, the enlarged spleen, the coated tongue, the not infrequent intestinal symptoms may closely simulate typhoid fever. This type of fever has indeed been called *Subcontinua typhoidea* (Bacelli). Examination of the blood, in æstivo-autumnal fever, reveals infection with *Plasmodium falciparum* (*Laverania malarie*). As has been mentioned elsewhere, these parasites differ from those of tertian and quartan fever in that a greater part of their cycle of existence is passed in the vessels of the internal organs, the younger forms alone being observed in the



ipheral circulation. Towards the middle and latter part of the paroxysm immediately afterwards, small, refractive, ring-shaped, and amoeboid forms are to be found which gradually develop a very few, extremely, peripherally arranged pigment-granules. The ring-shaped bodies are often contained in shrunken or cremated, brassy-coloured corpuscles. Sometimes in these brassy-coloured elements the hæmoglobin retracts to the periphery of the corpuscle, forming a layer about the parasite. Gradually the number of pigment-granules increases, though, as a rule, only two or three fine bits of pigment are to be found in each parasite. Infections in which the organisms are arranged in well-defined groups may be extremely difficult to demonstrate any parasite in the peripheral circulation during the period immediately preceding the paroxysm. But infrequently in severe infections a few mature bodies, half the size of the red corpuscle, with a single central pigment block or clump, may be found at this period. Segmenting bodies are rare in the peripheral circulation. Aspiration of the spleen, however, may shew a great abundance of the mature forms with central pigment clumps or blocks, as well as segmenting bodies. This infrequency of the parasites just before and at the end of the paroxysm is a very important and characteristic point. After, and on the following day, small hyaline or early pigmented forms may be numerous. In the case of parasites with cycles of development of forty-eight hours or longer, the bodies are somewhat larger, and the pigment slightly more abundant than in infections with organisms having a shorter cycle, in which segmentation has been described, while the parasite is still free from pigment (Marchiafava). After the process has lasted from five days to two weeks, gametes, large ovoid and crescentic forms, with collections of coarse, centrally arranged pigment-granules, are usually present. A highly important diagnostic point in the æstivo-autumnal fevers is that, although at and just before the onset of the paroxysm, the parasites may be present in the peripheral circulation in very small numbers, yet phagocytes containing blocks of pigment are usually fairly abundant. The diagnostic importance of these elements should not be overlooked. In suspected cases in which organisms are not found in the fresh blood, examination should always be made of dried specimens stained by one of the modifications of Romanovsky's method. The blue rings with deeply staining chromatin dots are much more quickly recognised than the delicate hyaline bodies in the fresh blood.

**Pernicious Fevers.**—Tertian and quartan fevers, when untreated, usually pursue a favourable course, terminating in spontaneous recovery, and, although frequent relapses may bring about grave cachexia, acute symptoms of a dangerous character are of the utmost rarity. The same cannot be said of æstivo-autumnal fever, which, if untreated, gives rise in many instances to the gravest manifestations. The rapidity of the multiplication of the parasites, their especial malignancy (from the standpoint of their supposed toxic influence), and the tendency toward the involvement of certain vital organs, bring about the malignant manifestations



commonly termed "pernicious." These symptoms rarely or never appear with the initial paroxysms; they are the result of neglect of treatment. Pernicious fever occurs in various types.

*The Comatose Type.*—After several paroxysms, which may or may not have shewn a tendency to increase in severity, a fresh attack occurs, beginning often with a period of excitement, perhaps delirium, nausea, and vomiting, and followed rapidly by drowsiness, somnolence, or genuine coma. There may be restlessness and jactation; the respiration may be quiet, loud, and stertorous, or of the Cheyne-Stokes character. The pulse, at first full and slow, becomes towards the end rapid, feeble, and irregular. The skin is often hot and dry; the pupils dilated, contracted, or irregular. The conjunctivæ are usually injected, the tongue dry and coated. Slight jaundice of the skin and conjunctivæ is an important sign. There is usually moderate anæmia. The deep reflexes may be present or absent. Local spasms may point to a special localisation in the central nervous system of changes due to the focal accumulation of parasites. The spleen is usually palpable. During the attack the temperature is usually high, sometimes above 106° F.; as it falls the patient gradually regains consciousness. Defervescence may be associated with active delirium, lasting perhaps (Marchiafava and Bignami) for several days and ending fatally. Again, an improvement may last but a few hours, being rapidly followed by a fatal recurrence. Coma may last a few hours or for as long as four days; in favourable cases it slowly passes off with defervescence and the sweating stage, although for some time after the attack the patient is usually dull, stupid, and apathetic. Should a succeeding paroxysm occur, it is generally fatal. Marchiafava and Bignami have observed cases in which the coma lasted from four to five days, death occurring at a time when the parasites had almost completely disappeared from the circulation, both peripheral and central. In these cases definite organic changes (punctiform hæmorrhages) are usually present in the central nervous system.

*Other Cerebral and Spinal Manifestations.*—The pernicious paroxysm may be associated with active, maniacal delirium, and in some instances tetanic convulsions have been observed. In children and young people the manifestations may simulate meningitis. Well-marked bulbar symptoms are not uncommon, and in a case of this kind Marchiafava demonstrated special involvement of the medulla at the necropsy. Disturbances of speech are not unusual. Transient hemiplegia, aphasia, or amaurosis may occur. Marked vertigo with symptoms, especially of the cerebellar type, are not infrequent; while in a number of instances a group of symptoms imitating disseminated sclerosis has been described (Torti and Angelini). Bastianelli and Bignami have reported a case with symptoms closely resembling those of so-called electric chorea. An interesting example of tetany occurring with the paroxysm was observed by Albert.

*Choleric Pernicious Fever.*—The special localisation of grave æstivo-autumnal infections in the intestinal tract may result in symptoms

four cases it was subnormal during the last two days of life. It is, however, usually clear almost to the end. As a result of fever and the quiet, listless condition of the patient, the early onset of an algid paroxysm may be entirely unnoticed. In one of our patients who had walked to the out-patient department died six hours after admission. The paroxysm may be associated with sanguineous vomiting and severe epigastric pains—*cardialgic fever*. Soulié and Gillot have recorded a case simulating peritonitis. A patient was admitted to the hospital in collapse, history of melæna on the preceding night. He was very ill, and could give a satisfactory account of himself. There was vomiting; it was peritoneal; the abdomen distended and exceedingly tender. Everything pointed to peritonitis, following a typhoid perforation. Examination of the blood, however, shewed numerous æstivo-autumnal parasites. The patient recovered promptly on vigorous treatment with quinine. Vomiting, polycholia, and jaundice may be prominent and make up the so-called *bilious* paroxysm. Cases in which the fever is accompanied by great dyspnoea, thoracic pain, cough, blood-streaked sputa, and evidences of acute bronchitis, have been classed by some as *pneumonic pernicious fever*. Pernicious symptoms—prostration, etc.—may develop in association with a great accentuation of the late stage of the paroxysm—*sudoriferous or diaphoretic paroxysm*. Cases of malignant or malignancy are cases with manifestations of purpura febrilis—*the hæmorrhagic paroxysm*.

Examination of the blood in pernicious fevers reveals, in the great majority of cases, very large numbers of æstivo-autumnal parasites. The multiplication of plasmodia may be so great as to justify a fatal

Thus, a patient, seen shortly after a severe malarial attack, was perfectly conscious, and though weak and exhausted,

have wholly disappeared from the blood of the ear or finger. The presence, common in pernicious fever, of larger forms of the parasite with central pigment-blocks, is specially important, and, according to Bastianelli and Bignami, is absolutely diagnostic of a great accumulation of plasmodia in the internal organs. The presence in the peripheral circulation of macrophages containing larger and smaller clumps of pigment, and often fragments of red corpuscles, which, in my experience, is the rule in pernicious fever, may be a sign of great importance. I have found these bodies in considerable numbers in cases of pernicious fever in which the parasites were not especially abundant.

**Combined Infections.**—Infections with more than one species of the malarial organism at the same time are not uncommon. The usual combination is that of tertian and æstivo-autumnal parasites. One species of organism generally prevails, and is responsible for the manifestations. In such infections alternating relapses have been described, due first to one and then to the other species of parasite, the course of events suggesting that the prevalence of one parasite has some inhibitory influence on the growth of the other. With the decadence of one species, however, the other begins to develop, producing symptoms in its turn. Occasionally, however, active groups of parasites of different species may exist simultaneously in the blood, and give rise to a complicated clinical picture. Marc has reported an interesting case of combined tertian and quartan infection. Wood of Wilmington, North Carolina, has shewn me preparations of the blood of a similar case.

**Relapses: Fevers with long intervals.**—Untreated malarial fever, unless it become pernicious, commonly undergoes spontaneous improvement, and in some instances, especially in tertian infections, the recovery may be permanent. Usually, however, even after fairly vigorous treatment during the original attack, there are relapses which may follow in more or less regular cycles. These may be divided into relapses occurring after short intervals and those following at longer periods (Caccini).

*Relapses at short intervals* are apt to recur after periods approximating in time to the duration of the ordinary incubation; they are observed in tertian fever at intervals of from five to eighteen days, and in æstivo-autumnal fever at intervals of from five to nine days. In quartan fever, in which relapses are especially common, there seems to be no particular rule as to the time of outbreak, which is generally traceable to some definite exciting cause. Caccini has never observed spontaneous recovery in quartan malaria. These relapses appear to be due to the fact that, as a result of treatment or through natural powers of resistance of the human organism, so great a part of the infecting group of parasites is destroyed that a period, which approximates closely to that of the ordinary incubation, must be passed through before it reaches again a size sufficient to produce distinct paroxysms. In some instances the relapse consists of a single attack, after which a period of time practically or exactly equal to the previous intermission may elapse before a second

recurrence. This sequence of events may continue for some time, giving rise to so-called fevers with long intervals. Carducci finds that in aestivo-autumnal fever the usual period of intermission is about seven days. In such cases the persistence through long periods of time of a low grade of infection may produce grave cachexia. Relapses of this sort are commonest in children, especially in those under five years of age, this may be due to the lessened resistance of the infantile organism or to the greater difficulty of carrying out efficient treatment. Relapses at short intervals, though frequent in all forms of fever, are commonest in tertan infections, probably because, on account of the mildness of the manifestations, proper treatment is often neglected.

*Relapses after long Intervals*—Another variety of relapse occurs after periods of from several months to over a year. These outbreaks appear to depend upon various exciting causes, such as insufficient food, articles of diet which produce disturbances from special individual idiosyncrasy, gastro-intestinal disturbances, hard physical labour, mental strain, exposure to cold or wet, change in temperature or climate, trauma, surgical operations, pregnancy and parturition, infections, such as pneumonia and enteric fever, and drugs (tuberculin, iodide of potassium). Relapses after long periods of time are especially common in tertian fever less so in aestivo-autumnal infections. Relapses of tertian fever rather in the malarial season in temperate climates. In the intermissions between such relapses the patient appears perfectly well. No parasites are found in the circulation, and there is no anaemia. Treatment by quinine during the intermission has no effect whatever in preventing the relapse.

The form in which the parasites persist throughout these long periods, and the part of the body in which they are hidden, are entirely unknown. It is not impossible that these late relapses may be due to parthenogenetic segmentation of macrogametes, such as has been described by Scandinn. We have seen appearances exactly similar to his. Italian observers point out that in the malarial epidemic relapses are always more frequent than primary attacks.

While recrudescences are especially frequent in quartan fever, the remarkable tenacity of which has been known for generations, relapses at long intervals are not common. The infection, though mild in its manifestations, persists for considerable periods of time, breaking out at intervals under any provocation, such as those above mentioned.

*The Urine in Malaria*.—There are no constant variations in the amount of urine in malaria. The greatest quantities are passed during the early parts of the paroxysm. A post malarial polyuria is common, beginning a few days after the disappearance of fever, and lasting sometimes as long as thirty days; this is more marked after tertian and quartan than after aestivo-autumnal fever. The colour of the urine is usually high, depending on the increased amount of urobilin. There is no characteristic change in the acidity. The specific gravity varies inversely with the amount; it is often relatively high in post-malarial

polyuria. The total nitrogen excretion is increased both during the acute stages of the illness and in the post-malarial polyuria, but the uric acid is not increased. The chlorides are present in normal proportion, being increased during the paroxysms, thus contrasting with the condition in fevers associated with local inflammatory processes; they are markedly increased in post-malarial polyuria. The elimination of sulphates corresponds closely to the variations in the excretion of nitrogen. The phosphates are often increased in quantity, but, unlike the other solid constituents, they are diminished during the febrile paroxysm; they are much increased in post-malarial polyuria. In the regularly intermittent fevers, tertian and quartan, a trace of albumin was present in 38.6 per cent of 352 cases in the wards of the Johns Hopkins Hospital. In æstivo-autumnal fever it was more frequent, occurring in 58.3 per cent of 165 cases. In the great majority of instances there was only a slight trace. In many of the cases in which albumin is found occasional hyaline casts may be detected in the sediment. In pernicious fever traces of bile may be found.

**Cause of the Malarial Paroxysm.**—There has been much speculation as to the cause of the remarkable periodical paroxysms of malaria. Not only the character of the manifestations themselves, but the degenerative changes found in many organs—brain, nerves, liver, kidneys—suggest that the access is associated with the presence of some circulating toxic substance or substances. The definite coincidence of the paroxysm with the fission of a generation of organisms has led most observers to assume that the poison, whatever it may be, is set free by the parasites at their time of segmentation. All attempts to isolate a specific toxic substance have so far been without result.

**Sequels.**—*Results of frequently relapsing or repeated Infections.* *Cachexia.* *Masked or Larvate Malarial Infections.*—Frequent relapses or often repeated malarial infections may give rise to a great number of clinical manifestations. In prolonged cases the patient may be reduced to a state of grave cachexia, the characteristic features of which are anæmia, great enlargement of the spleen, and a liability to anasarca and dropsy. In an advanced case the condition of the patient is truly pitiful. The emaciation, the dead, sallow, anæmic, earthy grey complexion, the sunken eyes, the listless, feeble air, the large spleen, and the œdema make a most characteristic and easily recognisable picture. In children growth is often retarded, and well-marked infantilism may result (Cardarelli). *Anæmia* is among the commonest and most important sequels. Changes in the blood arise not only from the destruction of corpuscles in the individual malarial attack, but also as a result of changes in the blood-forming organs, as well as in other vital parts. The moderate anæmia which follows the first acute attacks is generally compensated for by active regeneration. In long-continued or recurrent infections, however, pronounced anæmia may result. This is usually of the type of an ordinary secondary anæmia, the colour-index of the red corpuscles being reduced, and the leucocytes diminished in number.

with a rather high percentage of mononuclear elements, especially of the large mononuclear variety. Nucleated red blood corpuscles (normoblasts) are present. Bignami and Dionisi and Ewing have described cases pursuing an unfavourable course, in which the blood presented the characteristics of the megaloblastic type of pernicious anemia, as well as rapidly fatal anemias with a diminution in the number of leucocytes, an excessive percentage of small mononuclear elements, and an absence of nucleated red corpuscles—aplastic anemia. *Malarial hemoglobinuria* is described on p. 289.

Among the cutaneous manifestations in chronic cases, especially when cachectic, is *purpura*, which may appear as a severe or even fatal *purpura hæmorrhagica* (Ascoli). The peculiar *earthy colour of the skin* is so characteristic as to be often recognisable by the skilled observer. A remarkable phenomenon, occurring especially in chronic cases, is *anasarca*, which may, as Ascoli has pointed out, simulate sometimes the edema of nephritis, sometimes that of cardiac failure, although the urine may be quite free from albumin. Common in cachectic subjects, such edema may appear in individuals in relatively good condition. An instance of this sort came under my observation some years ago. A man of about fifty entered the hospital in fairly good condition with well-marked edema of the legs, and slight ascites, without apparent cause. There was no reason to suspect any disease of the heart, liver, or kidneys. Some days after admission the patient had a relapse of tertian malaria, a clear history of which had not been previously obtained. With rest and tonic treatment the edema generally clears up. *Multiple cutaneous gangrene* is sometimes met with. A remarkable case of this nature has been reported by Prof. Osler. Dr. E. J. Wood of Wilmington, North Carolina, tells me that he has, in the last few years, seen several similar cases, in all of which the coincidence or immediately preceding existence of malaria has been proved by examination of the blood.

*Nephritis*.—Acute nephritis is not an uncommon sequel, occurring in 15 per cent of 1832 cases analysed at the Johns Hopkins Hospital. Rare in tertian and quartan infections, it is by no means infrequent in *tertio-autumnal fever*. There is nothing remarkable in the character of the disease, which pursues the course of an ordinary acute toxic nephritis. Of 26 cases of malarial nephritis 14 recovered; 4 died; in 9 the result was doubtful; in 2 chronic nephritis followed. We have since seen several additional cases of chronic nephritis of undoubted malarial origin.

*Gastro-intestinal Tract*.—Diarrhœa and dyspepsia are common in cachectic patients, but there are no especially characteristic gastro-intestinal manifestations.

*Liver*.—As has been described in the section upon pathological anatomy, distinct changes in the liver associated with enlargement and chronic perilobular hepatitis often follow repeated malarial infections. These changes, however, give rise to no characteristic clinical manifestations. While there is little anatomical evidence that malaria induces hepatic changes capable of producing the clinical manifestations of portal



cirrhosis, some authors insist on the occasional clinical sequence of atrophic cirrhosis of the liver after malaria (Kelsch and Kiener, Lodigiani, Phillips).

*Nervous System.*—The grave nervous phenomena accompanying pernicious paroxysms are usually associated with fever. Sometimes, however, the paroxysm may be represented by the nervous manifestations alone, fever being almost or entirely absent. After pernicious paroxysms the nervous phenomena clear up, as a rule, rather slowly; sometimes, indeed, they may persist for considerable periods of time. In chronic or frequently repeated attacks, especially of æstivo-autumnal malaria, the patient may present nervous phenomena of great variety and persistence. The commoner of these manifestations—vertigo, motor instability, tremor, ataxia of the cerebellar type, dysarthria, increasing as they do in pernicious paroxysms to hallucinatory delirium, coma, and even convulsions—are, as Ascoli has well pointed out, in many ways analogous to those observed in alcoholism. The dulness, the uncertain memory, the listlessness, the apathetic condition, the tremor, the slow, uncertain speech of the cachectic patient, are very similar to the manifestations of chronic alcoholism. The psychical phenomena, also, are usually of a confusional type with a tendency toward hallucinatory delirium. Slow, hesitating speech, marked muscular weakness, or sometimes increased muscular excitability with exaggerated reflexes, are common. In a number of instances a clinical picture simulating that of *insular sclerosis* has been described (Torti and Angelini, Panichi, Bignami and Bastianelli, Spiller). Most of the hemiplegias occurring in connexion with malaria, as in one of our cases, are probably in individuals with pre-existing vascular changes, in whom the paroxysm has acted as the exciting cause for the rupture or thrombosis.

Neuralgias, especially of the fifth nerve, may occur in chronic malaria, although intermittent facial neuralgia is much too often ascribed to paludism. Neuritides of the type of ordinary toxic multiple neuritis have been described by a number of observers (Eichhorst, Saquepée and Dopter, Schupfer, Fajardo and Couto, Luzzatto). Necropsies in the cases of Fajardo and Couto and Luzzatto shewed widespread and extensive parenchymatous neuritis. In the latter case degenerative changes in the anterior horn cells were also found. Cachectic subjects seem to be especially liable to neuritis from other recognised toxic causes. Deafness from neuritis of the auditory nerve has been described, although some of these instances are probably due to the administration of quinine. Optic neuritis, followed by atrophy, retinal hæmorrhages, and retino-choroiditis, have been observed. Bindi reports an instance of angioneurotic œdema in a cachectic patient. In the reported cases of epilepsy of supposed malarial origin, it is quite possible that malaria acted only secondarily, as the exciting cause in a predisposed individual. Neurasthenia and hysterical conditions may follow malaria as in the case of any severe infection. Post-malarial psychoses are rare. Marchiafava and Bignami describe a case of acute maniacal delirium with a fatal result following a pernicious attack, while



conditions of slight mental confusion with hallucinations may last for a week or two after malignant paroxysms. In one of our cases the patient remained in a depressed, confused condition with hallucinations for several months after an attack of tertian fever.

**Masked Malarial Infections.**—Before the discovery of the parasite a great number of conditions having no relation to the disease were described as masked or larvate malaria. With our present knowledge such confusion should not exist. It has, however, long been known that parasites may be present in the circulation for considerable periods of time without causing symptoms which are definitely recognised as due to malaria. Latent infections are especially common among the natives of the tropics (Koch, Stephens and Christophers, Craig). Some of these cases occur in individuals who have not been regularly or properly treated. In others, apparently because of the resistance of the organism, or from other causes, the infection never develops sufficiently to provoke frank, characteristic paroxysms.<sup>1</sup> Moreover, as has been already mentioned, grave, even pernicious, manifestations of a nervous character may occur with normal or but slightly elevated temperature. In 395 out of 1267 cases of malaria studied by Craig in the army hospital at San Francisco, the symptoms were such that malaria was not recognised before the demonstration of the parasite in the blood. These facts emphasise the importance of regular examinations of the blood, especially in malarious regions or where there is the possibility that the patients may have been subjected to infection.

**Complications.**—Pneumonia is so frequently a complication or sequel of malaria, and is so common in cachectic patients that, previously to the discovery of the parasite, it was often regarded as of malarial origin. The diminished resistance in cachexia no doubt favours the incidence of pneumonia as it does of any severe secondary infection; moreover, pneumonia may occur as a complication of a severe malarial attack, just as it may in enteric fever. The malarial infection may produce active symptoms during the course of the pneumonia, though it commonly remains latent during the attack, breaking out with convalescence. We have observed combined infections of pneumonia and malaria in several cases in the wards of the Johns Hopkins Hospital. The so-called *pneumonic* paroxysm has no connexion with true pneumonia.

**Enteric Fever.**—Much has been written about the co-existence of malaria with enteric fever. In the great majority of instances the malarial outbreak occurs during convalescence from the enteric fever, though occasionally the two infections may exist simultaneously in an active stage, as in a case reported by Craig. The once prevalent belief that a special form of fever existed, resulting from a combination of the typhoid and malarial poisons, to which the name *typho-malaria* might properly be given, is without foundation.

<sup>1</sup> Craig remarks that the presence of intracorporal conjugation of the parasites, a process which, in common with Ewing, regards as essential for the maintenance of an acute infection, are absent in latent malaria.

*Dysentery* and malaria may co-exist, and cachectic patients are unquestionably disposed to intestinal disorders. The combination of malarial infection with dysentery of the amoebic type is not uncommon. There is no such thing, however, as a specific malarial dysentery. Instances of combined infections of malaria with *cholera*, *small-pox*, and a number of other acute diseases have been described. They present, however, no characteristics worthy of special mention. *Tuberculosis* and malaria were formerly thought to be antagonistic. The discoveries of recent years, however, have proved not only that tuberculosis does not exclude malaria, but that the existence of paludism in a tuberculous patient has a distinctly deleterious influence upon the course of the case, favouring the increased activity of the latter disease. *Post-partum* and *post-operative* relapses of malarial fever are not uncommon. Inasmuch as such relapses are not confined to malarial districts and may assume a pernicious character, careful examination of the blood should always be made in the presence of anomalous symptoms after operation or in the puerperium. It should, however, be remembered that the terms *post-partum* and *post-operative* malaria have been greatly abused. It is probably fair to say that a large proportion of the cases reported in literature represent septic infections.

**Diagnosis.**—Since the discovery of the parasite the diagnosis of malaria has become a relatively simple matter.

*Tertian and Quartan Infections.*—In single tertian or quartan fever the characteristic intermittent paroxysms with the regular stages of chill, fever, and sweating justify of themselves a probable diagnosis. Herpes, anæmia, the earthy, greyish, slightly jaundiced colour of the skin, and the palpable spleen also help in the diagnosis.

The intermittent febrile paroxysms of *pulmonary tuberculosis*, so frequently confounded with malaria, are rarely as regular, and are usually of much longer duration. They occur generally in the afternoon, while the malarial paroxysm begins more commonly in the morning hours. The chills, fever, and anæmia associated with infective endocarditis, septicæmia, and pyæmia may simulate malaria; the paroxysms are, however, irregular and shorter, two or three occurring sometimes in twenty-four hours. In two instances of influenza I have seen remarkably regular tertian and quotidian paroxysms closely resembling those of paludism, but the thoracic symptoms were characteristic, and influenza bacilli were demonstrated in the sputa. The essential procedure in diagnosis is the *examination of the blood*,<sup>1</sup> which reveals the characteristic parasite. Another very important point is the constant absence of leucocytosis in tertian and quartan malaria, and its presence in most of the conditions which may give rise to a mistake in diagnosis. The presence of an appreciable leucocytosis is strong evidence against the existence of uncomplicated malarial fever. When but few parasites are to be found, pigment-

<sup>1</sup> In this connexion I venture to quote a statement made elsewhere: *It is impossible to make reliable examinations of the blood for malarial parasites without first being familiar with the ordinary appearances of normal blood and the commoner pathological changes.*

bearing leucocytes may be an important aid in diagnosis especially at the time of the paroxysms. The skilled observer can usually distinguish malarial pigment from extraneous particles. The differential diagnosis between tertian and quartan infections is best made by examination of the fresh, unstained specimen of blood. The tertian organisms are larger, paler, more actively amoeboid. The pigment, especially in the younger forms, is in smaller particles and more actively motile. The merozoites in the segmenting organisms are more numerous (15-30) and are so regularly arranged. The surrounding corpuscle becomes demorganised and expanded with the growth of the parasite. The quartan organism is smaller, more sharply outlined, less amoeboid, slower in its movements; its pigment is coarser and less motile, and often more peripherally placed. The merozoites are less numerous (6-12) and more regularly arranged, the surrounding corpuscle is apt to retract about the parasite, and becomes of a deeper colour. The same characteristics may be made out, though with somewhat less distinctness, in the stained specimen. In quartan fever the organisms are found with great frequency at all stages of development. In tertian fever they are somewhat less frequent in the blood at the period immediately preceding and during the paroxysm than during their earlier stages.

**Response to the therapeutic test.** The immediate disappearance of the fever after treatment with quinine, is a strong, though not positive evidence of its malarial origin. The persistence of intermittent fever after 12 days treatment with quinine excludes malaria. Multiple and complicated infections may be readily recognised by examination of the blood. The simplest, and in many instances, the most satisfactory method of examining the parasite is in specimens of the fresh blood which, with the portable microscopes now available, can be readily examined at the bedside. If this be impossible the preparation of dried specimens stained by one of the different forms of the Romanovsky stain, especially that of Leishman and its various modifications (Wright, Hastings, Goldhorn), is an easy method of diagnosis. The blood should be examined before the beginning of treatment. A few doses of quinine often cause the disappearance of parasites from the peripheral circulation or so far reduce their number as to interfere greatly with diagnosis.

**Intermittent Malaria.** In this form the diagnosis is not so simple. When the paroxysms are distinctly intermittent, paludism may be at once suggested by the raised temperature, the characteristic change in the complexion, the jaundice, the frequently complicating herpes and the enlarged spleen. The symptoms, however, may be obscure. The disease is most commonly confounded with *enteric fever*. The intermittent or regularly remittent character of the fever may become evident only after long observation of carefully kept charts, while the absence of chills, the pains in the head, loins, and extremities, the general apathetic condition of the patient, the coated tongue and the enlarged spleen all exclude enteric fever. The examination of the blood usually settles the question. The leucocytes are normal or reduced in number in both

infections, but in malaria æstivo-autumnal organisms as well as pigment-bearing phagocytes can nearly always be found. A special diagnostic difficulty met with in æstivo-autumnal fever is the small size of the parasites and the absence of pigment which, to the unskilled observer, renders them difficult to recognise in fresh blood. Again, artifacts and degenerative changes in the blood-corpuscles are often confusing.<sup>1</sup> At maturity the æstivo-autumnal parasites are very scanty in the peripheral circulation, collecting usually in the internal organs, so that at a period immediately preceding and during the early part of the paroxysm, if a single group be present, but few organisms may be found. It is very important, therefore, in any doubtful case, to prepare stained specimens of blood. The characteristic ring-body, with its striking chromatin-granule, is much more readily distinguished in the stained specimen than in the fresh blood. If, in a suspected case, no parasites are found in an examination made early in the paroxysm, the procedure should always be repeated some hours later, when the result will probably be positive. Like Marchiafava and Bignami I have never found it necessary to puncture the spleen for diagnostic purposes. The procedure is, moreover, by no means free from danger in unskilled hands. In cases which have lasted over five days the frequent presence of the sexually mature forms, the large ovoid and crescentic bodies, is of great diagnostic help. It is, however, in the *pernicious fevers* that confusion is most likely to arise. The comatose paroxysm may be mistaken for sunstroke, uræmia, or cerebral hæmorrhage. The differential diagnosis from sunstroke may be extremely difficult, especially in cases in which the latter occurs in an individual already suffering from mild or chronic malaria. Jaundice, anæmia, and enlarged spleen would suggest malaria, while hyperpyrexia would be rather in favour of sunstroke. Although in some cases with cerebral manifestations there may be no great excess of parasites in the peripheral circulation, they are almost always present in sufficient numbers to allow of a speedy diagnosis. The frequency of pigment-bearing macrophages is a point of great importance in the diagnosis of pernicious fever; thus, in a case of comatose paroxysm, in which the number of parasites was relatively small, I found numerous pigmented macrophages. As pointed out by Marchiafava and Bignami, these persist in the circulation for some days after the parasite has disappeared as a result of treatment. The tetanic, meningeal, eclamptic, and hemiplegic types of malaria can also be recognised by the condition of the blood. In some instances, especially in an algid paroxysm or in afebrile attacks with grave nervous phenomena, the disease may be wholly unsuspected in the absence of systematic examination of the blood. The hæmorrhagic paroxysm may suggest yellow fever, which, indeed, it may complicate. The disproportionately slow pulse in yellow fever is an important diagnostic point, while the

<sup>1</sup> Nearly every year articles appear in reputable journals describing as a "new variety of malarial parasite" the peculiar navicular bodies with rotatory motion about a central axis commonly observed in red blood-corpuscles. Incidentally the same structures have been described as parasites of measles and of yellow fever.

quantity of albumin in the urine is usually much greater than in malaria. Examination of the blood is sufficient to determine the presence of the malarial disease, although, as demonstrated in the recent epidemic in New Orleans, this may not exclude co-existing yellow fever.<sup>1</sup>

*Chronic Malarial Cachexia.*—The diagnosis of chronic malarial cachexia is rarely difficult if the history of the patient and the conditions under which he has lived be taken into account. It must be distinguished from secondary or primary anæmia, leukæmia, and the various types of splenomegaly—the so-called primary splenomegaly—splenic anæmia, or Banti's disease, and especially from kala azar. The enlarged spleen, the severe anæmia, the liability to hæmorrhages and dropsical effusions, common to these various conditions, may render the diagnosis rather difficult. Leukæmia, of course, can readily be excluded by examination of the blood. The same, however, cannot be said of primary splenomegaly or Banti's disease, in which the type of anæmia is closely similar to that usually observed in malarial cachexia, while hepatic enlargement is common in both maladies. In such cases one must depend largely upon the history of the case. A febrile recurrence, with the presence of malarial parasites in the circulation, or the discovery of gametes of the æstivo-tropical organism, settles the diagnosis. Kala azar (*vide* p. 226) may be suspected in a patient coming from a district such as Assam, where it is known to exist, who has an enlarged spleen and liver, fever unrelieved by quinine, and no malarial parasites in his blood. Splenic puncture would reveal the presence of the Leishman-Donovan body. On the other hand, kala azar may be complicated by malaria, and the most decisive test—splenic puncture—is not without danger. There is nothing characteristic in the *nephritis* of malarial origin.

*Masked Malarial Infections.*—In regions in which malaria is common, among patients who come from malarious localities, examination of the blood in all doubtful or unusual manifestations should never be neglected, as this may lead to the discovery and relief of a considerable number of unsuspected cases of malaria (*cf.* p. 267).

*Prognosis.*—The prognosis of *tertian* and *quartan* infections is almost always good; I know of but two recorded instances of pernicious fever occurring in tertian malaria (French, Ewing). Spontaneous recovery is not infrequent in tertian fever. Frequent relapses are, however, the rule, and unless thorough and persistent treatment be carried out, grave cachexia may develop. Quartan fever, though benign in its manifestations, is peculiarly tenacious, relapses often occurring, under slight provocation, through long periods of time.<sup>2</sup> Under treatment with quinine recovery is universal.

<sup>1</sup> Lanoux of New Orleans has shewn me several interesting charts of combined infections of malaria and yellow fever; his communication upon this subject will appear shortly.

<sup>2</sup> Thus Galen (*Glaucon*, ix.; *Kühn*, xi. 25) says: "Among the intermittents the shortest and most tractable is the tertian; the longest, but that which is *per se* free from danger, is the quartan."—ἐπὶ μὲν οὖν τοῖς διαλείπουσιν ὀξύτατος τε ἅμα ἐπιεικέστατος ὁ τριταῖος ἐστι· μακρότατος δὲ καὶ ἀκίνδυνος ὅσον ἐφ' ἑαυτῷ ὁ quartan.



In *æstivo-autumnal fever* the prognosis depends upon the gravity of the infection and the duration of the case. If untreated, spontaneous recovery may occur, but the development of grave cachexia is common and pernicious manifestations are by no means unusual. If the diagnosis be made early, and thorough treatment with quinine be initiated, the prognosis is perfectly good. If, however, *pernicious symptoms* have developed, the prognosis is always extremely grave. An absolutely favourable prognosis cannot be given until at least forty-eight hours after the beginning of treatment. Not infrequently the subsidence of one paroxysm may be rapidly followed by a second, which, despite treatment, may prove fatal. If, however, this paroxysm be recovered from, a favourable prognosis may be given in most instances. The presence of an excessive number of parasites in the peripheral circulation in the interval following a pernicious paroxysm is of grave importance. The converse, however, does not justify a corresponding good prognosis inasmuch as there may be a relative infrequency of parasites in the peripheral circulation in cases of grave cerebral manifestations (vide p. 261). Nor does the disappearance of the parasites from the blood under treatment of itself justify a favourable prognosis, for, despite this, a pernicious paroxysm may continue to a fatal termination. The prognosis in *chronic malarial cachexia* is usually good as far as life is concerned, if the condition have not lasted too long, and if the patient be in a position to take proper therapeutic and prophylactic measures. Removal to a healthy non-malarious district or proper treatment, even at home, usually be followed by recovery. Without such measures, however, though rarely dying from the malarial cachexia alone, the patient falls prey sooner or later to some secondary infection—chronic nephritis, perhaps, amyloid disease. The prognosis in *malarial nephritis* is as a rule good, although chronic progressive changes may occur. The same is true of the remarkable nervous phenomena which may follow malaria. With proper treatment is followed, in the great majority of instances, by permanent recovery, yet such cases as that of Spiller suggest that permanent changes may remain.

**Treatment.**—The treatment of malaria may be divided into (1) general management, (2) medicinal measures.

*General Management.*—Wherever possible, the patient should be confined in bed until all febrile manifestations have subsided and parasites have disappeared from the peripheral circulation. Unfortunately, it is not always easy to enforce this in mild cases. In some tertian infections rest in bed, with proper diet and care, are all that is sufficient to effect a temporary or even a permanent cure, and there is a decided difference between the course of tertian and quartan infection in individuals who keep about their business and in those who submit to a period of a week or several days to thorough treatment. Rest in bed should be insisted upon in all cases of *æstivo-autumnal fever*.

During the short cold stage of the paroxysm the patient should be made as comfortable as possible. Warm coverings are allowable, even

the fever have already begun. Hyperpyrexia, especially in æstivo-autumnal fever, where the paroxysms are of longer duration, should be met by cold sponging or tub-baths.

In tertian and quartan fever there is, as a rule, no occasion for modifying the diet. In the more severe æstivo-autumnal fevers the lack of appetite and general prostration of the patient may render a liquid or soft diet, consisting of broths, soups, milk, raw or soft-boiled eggs, and the like, more convenient. If there be no gastro-intestinal symptoms, solid food may be given if the patient so desire. Abundance of water should be allowed.

*Medicinal Treatment.*—We are fortunate in possessing a drug which exercises a true specific action on malaria. All malarial infections yield to quinine, provided treatment be instituted in time. The effect of the drug depends upon its poisonous action upon the parasites. As early as 1867 Binz correctly concluded that the efficacy of quinine in paludism depended upon its action as a protoplasmic poison upon some lower organism, an hypothesis based upon his experience concerning the influence of quinine upon the infusoria. Various observers (Golgi, Mannaberg, Romanovsky, Marchiafava, Bignami, Baccelli, Lo Monaco, and Panichi), who have studied the changes occurring in parasites after the administration of quinine, confirm Laveran's observation that the organisms rapidly disappear after the drug has been taken. This is true of all forms of the malarial parasite excepting the gametes, especially those of the æstivo autumnal organism (crescentic and ovoid forms), which may persist for weeks or, rarely, for months during treatment. These bodies, however, are, in ordinary circumstances at least, incapable of giving rise to the asexual cycle of the parasite, and are, therefore, harmless while in the human body. Quinine exercises its action rapidly on the merozoites during their extra-corpuscular and earlier intra-corpuscular stages. The mature schizonts are more resistant. If quinine be introduced into the circulation at about the time that the parasites have reached maturity, it will not prevent the segmentation of the ripening group, but it will destroy the young merozoites. If it be introduced into the circulation in sufficient quantities during or soon after the paroxysm, it will go far toward destroying the group of parasites which have caused the fresh infection. In order, then, to prevent the further development of a group of malarial organisms, quinine should be administered so as to be present in solution in the blood, at the time of segmentation or during the earlier part of the intra-corpuscular life of the parasites, that is, during the several hours before and during the paroxysm, and during the twenty-four hours immediately following it.

*Effects of Quinine upon the Human Being (Toxicæmism).*—In most individuals ordinary therapeutic doses of quinine are without seriously unpleasant consequences, producing, at the most, slight tinnitus aurium and deafness. Larger doses produce more pronounced deafness, vertigo, and headache, which may be severe. This is followed in graver cases by



great muscular weakness, tremor, staggering gait, dilatation of the pupils, amblyopia, amounting sometimes to total blindness, and, if the dose be large enough, finally convulsions and death. A number of cutaneous disturbances have been observed after quinine. Urticaria and scarlatiniform erythemas are common; the latter may be followed by desquamation. There are great variations in the susceptibility of different individuals to the toxic effects of quinine. Most patients are able to take doses up to grs. v. (0.325 gramme) without discomfort. Many, however, suffer from tinnitus aurium and headache with doses as large as from grs. x.-xv. (0.65-1 gramme); these symptoms are, however, transient and free from serious consequences. Occasionally patients are met with who, through individual idiosyncrasy, shew such a marked susceptibility to the action of quinine that its use is really impossible. In such cases gastro-intestinal symptoms of great severity, vomiting and purging, with marked urticarial or scarlatiniform eruptions, follow even the smallest doses. This susceptibility usually extends to the other cinchona derivatives. These cases are, fortunately, very unusual. I have met with but two. As is mentioned elsewhere (p. 294), quinine may, in rare instances, be followed by hæmoglobinuric fever. In the vast majority of cases in which patients assert that they "cannot take quinine," it will be found that the reason for the prejudice is that larger doses than necessary have been administered.

*Absorption and Elimination of Quinine.*—Quinine is rapidly absorbed: it is eliminated almost exclusively by means of the kidneys, the first traces appearing in the urine from 15 to 17 minutes after ingestion, and the greater part of elimination being accomplished within the first twenty-four hours. Mariani, however, has shewn that elimination continues for at least six days, one-half to two-thirds of the molecule of the alkaloid being demolished during its long sojourn in the tissues, so as to render its intermediate or final products unrecognisable. By intravenous administration a large quantity of quinine may be rapidly introduced into the circulation. I have seen cinchonism follow within a few minutes of the intravenous introduction of grs. xv. (1 gramme) of the acid hydrochloride. The intra-muscular injection of quinine has the advantage of more prolonged action, but this is less intense because of the notable quantity of the drug which is precipitated at the seat of injection. On this precipitation depends the paradox that to produce the same effect the dose of quinine must be larger when given by hypodermic injection than when given by the mouth. The absorption of quinine by the gastro-intestinal mucosa, although varying considerably in its rapidity, is usually complete. Fever does not interfere with its absorption except in the presence of special gastro-intestinal disturbances. The administration of quinine at the time of a meal seems to promote its absorption into the general circulation; if taken with food it appears to remain in the circulation in a somewhat higher proportion during the second and third days after the administration. The absorption of the less soluble preparations of quinine is at least as complete as that

of the more soluble salts. Quinine is cumulative in its action. On daily repetition, of a given amount, the fresh dose, entering the circulation, is added to the active residue of the former doses, so that the amount of quinine in the vessels arrives, within the first week, at its maximum limit, an amount such as is found in the first twenty-four hours only after the ingestion of a single dose equal to double that which is administered daily.

*Preparations and Manner of Administration.*—Of the various salts of quinine, the sulphate, the bisulphate, and the acid hydrochloride are most commonly used. The sulphate which is the cheapest salt is that in general use, and is thoroughly satisfactory for administration by the mouth. For hypodermic,<sup>1</sup> intravenous, or rectal administration, the more soluble forms, especially the acid hydrochloride, which is soluble in less than its own quantity of water, are more suitable. Quinine is best absorbed when administered in solution. The ordinary sulphate of quinine is easily rendered soluble by adding to the aqueous mixture one drop of dilute hydrochloric or sulphuric acid for each grain (0.065 gramme) of the salt. The taste is, however, very bitter and unpleasant. It can be somewhat masked by preparations of ginger or chocolate. Quinine may also be given in the form of capsules, tablets, or pills. The insolubility and common adulteration of quinine pills render their use unsafe. The administration of quinine tablets, such as those at present prepared by the Italian Government, has proved very satisfactory. A preparation known as enquinine, the ethyl ether of quinine carbonic acid, was placed upon the market a few years ago, and was recommended because of its tastelessness, it has a slightly bitter taste, but much less so than quinine. The dose is about a half again that of the sulphate. The Italian Government has used with great success in children a confection consisting of a mixture of chocolate and tannate of quinine. The tannate is so slowly absorbed that about one-fifth of the dose escapes with the feces. The dose should be somewhat more than twice that of the sulphate.

For hypodermic use the acid hydrochloride is the most satisfactory salt, although the bisulphate, which is soluble in nine or ten parts of water, will answer in an emergency. For intravenous administration we have used the following solution advised by Baccelli —

Acid hydrochloride of quinine	grs. xv. (1 gramme)
Chloride of sodium	gr 1½ 0.075 gramme)
Distilled water	5iss. (10 grammes)

The solution should be perfectly clear, and may be injected luke warm. The rectal administration of quinine is rarely necessary, and is rather unsatisfactory. Readily soluble salts should be used.

There has been much discussion as to the time at which quinine should be given. The answer depends upon the nature of the case, and

<sup>1</sup>In the hypodermic administration of quinine it is extremely important to introduce the drug deeply, intra-muscular injections are, indeed, safer. Superficial injections are often followed by painful and disfiguring necroses of the skin.

upon what one desires to accomplish. Single large doses of quinine by the mouth have the best effect if given three to four hours before the onset of the paroxysm. This does not prevent the impending paroxysm but, by destroying a large part of the group of organisms resulting from the segmentation of the mature generation, prevents its recurrence. It is at about the time of the paroxysm, immediately preceding, during, and following it, that the most vigorous treatment should be given in cases where such methods are necessary.

*Treatment of Tertian and Quartan Fever.*—The patient should be put to bed if possible. He should be assured that the results of treatment will be much more rapid and complete if he be willing to give up business for a few days. As a rule, it is quite sufficient to administer at regular intervals from grs. ii.-v. (0.12 to 0.325 grm.) of the sulphate of quinine three times a day, when possible after meals. Most tertian infections yield readily to doses as small as grs. ii. (0.12 grm.) three times a day. If the paroxysms have been severe it may be well to give a large dose of quinine, grs. x.-xv. (0.65-1 grm.), three to five hours before the next attack is expected. If the patient be seen during a paroxysm, a single dose of grs. v. (0.32 grm.), given immediately after defervescence, especially if followed by regular treatment, is usually sufficient to prevent further symptoms on the part of the segmenting group of parasites. After three or four days' treatment it is generally well to reduce the dose to grs. ii. (0.12 grm.) three times a day. This treatment should then be continued for at least three weeks. If the patient insist on remaining up and about, it may be necessary to continue larger doses, grs. v. (0.325 grm.) three times a day for as much as ten days, although, in most instances, grs. ii. (0.12 grm.) every four hours will be quite sufficient. Considerably larger doses are necessary when the patient is up and about than when he is in bed. The parasites disappear, usually, from the blood in from twenty-four to seventy-two hours after the beginning of treatment.

*Treatment of Estivo-autumnal Fever.*—The patient should be confined to bed until the fever has gone, and all traces of the asexual cycle of the parasites have disappeared from the circulation. In ordinary cases grs. v. (0.325 grm.) of the sulphate of quinine every four hours is a sufficient dose. This should be continued usually for about a week, the dose being gradually reduced until at the end of about ten days the patient is taking grs. ii. (0.12 grm.) of quinine three to four times a day. This treatment, as in tertian and quartan fever, should then be continued for at least three weeks. If relapses occur the dose should be increased again. If the paroxysms are severe, from grs. xv.-xx. (1-1.3 grm.) may be given at the outset and a few hours before the time of onset of the next expected recurrence.

Many observers recommend the intermittent administration of quinine, large doses of the drug, grs. x.-xxx. (0.65-2 grm.), being administered during the period of apyrexia from three to five hours before the expected paroxysms, for three or four days, grs. xv. (1 grm.) being repeated every six or seven days for a month or more afterwards.

Koch, in order to avoid relapses, advises the administration of grs. xv. (1 grm.) of quinine about every seven days for two days in succession, this treatment being continued for two months. Without the benefit of comparative statistics of our own, we have always been under the impression that the results of continuous treatment were more satisfactory than those of intermittent. The demonstration of the cumulative action of the drug by Mariani supports this method of treatment theoretically, while practically the prophylactic results of continued administration of the drug are more satisfactory (Celli). In *pernicious parasitisms*, most vigorous treatment is demanded from the onset. The acid hydrochloride of quinine should be given intravenously in doses of grs. xv. (1 grm.). This dose may be repeated if necessary, several times at intervals of four hours. The treatment will usually prevent any further dangerous manifestations from the segmenting generation of parasites, although it may be that a severe and even fatal paroxysm, due to another group of organisms, may occur within forty-eight hours. If the parasites remain present in large numbers, from grs. v.-x. (0.325-0.65 grm.), the sulphate or acid hydrochloride should be administered by the mouth when possible, every four hours during the first twenty-four hours following the paroxysm. If the patient remain unconscious, grs. xv. (1 grm.) should be given intravenously every six to eight hours, until the parasites begin to disappear from the blood, when the dose may be reduced to grs. v. (0.325 grm.) every four hours. In cases in which the patient asserts that he cannot take quinine, its administration in smaller quantity or hypodermically will usually accomplish the desired result without serious discomfort. Many patients who are unpleasantly cinchonised by doses of grs. x. (0.65 grm.), or even grs. v. (0.325 grm.) of the sulphate may be successfully treated if put to bed and given small amounts, grs. i.-ii. (0.065-0.2 grm.), at regular intervals. Quinine is contra-indicated only in those rare cases in which, through special idiosyncrasy, violent symptoms follow even the smallest doses. In these instances, which are happily rare, the patient should be removed to the most healthy region possible, absolute rest in bed should be insisted upon, and treatment with methylene blue employed.

Various other drugs have been used in the treatment of malaria. Few, however, deserve serious mention. Other *cinchona derivatives* such as *neochinin*, *cinchonidin*, *quinidin*, and *quinouin* have been recommended. Their efficacy is, however, far less than that of quinine, and the occasions for their use are limited.

Methylene blue was shewn by Guttman and Ehrlich to have a certain antimalarial action. My own experience confirms that of most observers that its efficacy is far below that of quinine, and uncertain. I have seen a relapse occur in bed, under continued treatment. I have, however, used it with success in tertian infection in an individual with an idiosyncrasy against quinine the patient having been previously removed to a healthy mountainous region and confined to bed. It may be given in capsules in doses of from grs. ii.-iii. (0.13-0.2 grm.) every four hours.

The strangury, which so commonly follows its ingestion, may be relieved by the administration of small quantities of powdered nutmeg. Phenocoll, about which much has been written by Italian authors, is of little value. The same holds good for the various arsenical preparations such as the arrhénal of Gautier.<sup>1</sup>

*Symptomatic Treatment.*—Various manifestations require symptomatic treatment. Vomiting, purging, excitement or delirium during the paroxysm may be controlled by hypodermic administration of morphine. In collapse during pernicious paroxysms, active stimulation must be resorted to. Alcohol, strychnine, or digitalin may be freely administered. During an algid paroxysm heat should be applied externally, while subcutaneous infusion of saline solution may be of value. Hyperpyrexia should be treated by cold sponging or baths. Anæmia following malaria should be treated by rest, diet, iron, and arsenic.

*Chronic Malarial Cachexia.*—The patient should, if possible, be removed to a healthy locality or at least placed at home in conditions such as to remove him from sources of further infection. An attempt should then be made to eliminate an existing infection and prevent relapses by the administration of small doses of quinine, grs. ii.-iii. (0.13-0.2 grm.) three times a day. If there be grave anæmia he should be kept absolutely at rest, and, as far as possible, out of doors. Exercise should be forbidden; the diet should be nourishing and simple; massage and hydrotherapy are often of considerable benefit. The anæmia should be treated by iron and arsenic. No preparations of iron are as good in the treatment of anæmia as the tinct. ferri perchloridi (tinct. ferri chloridi U.S.P.), and pilula ferri (pil. ferri carbonatis U.S.P.).

There is nothing specific in the treatment of post-malarial nephritis or of the various complications of the disease.

*Personal Prophylaxis.*—As the important question of public prophylaxis is considered by Prof. Ross, it is necessary to add a few words only, with regard to those personal measures which should be adopted by individuals who are obliged to live in a malarious locality. These measures are *mechanical* and *medicinal*. The former consist in precautions to avoid the bites of infected mosquitoes. In dangerous regions mosquito netting should always be carried, and *used in such a way that mosquitoes cannot enter*; for an improperly used net is as bad as none at all. If one be obliged to expose oneself among infected mosquitoes it is well

<sup>1</sup> There are few more discouraging illustrations of the weakness and fallibility of human judgment than those revealed by a review of the literature appearing every year concerning new remedies for malaria. He who attempts to study the therapeutical effects of a drug on malarial fever should read and take to heart the classical experience of Chomel quoted by Laveran from Trousseau and Pidoux. Chomel, wishing to test the properties of a powder of holly, chose twenty-two patients suffering from intermittent fever, but before giving the powder in question he put them under simple expectant treatment. Nineteen recovered spontaneously. Of the remaining three, one had a quartan fever and two quotidian. The powdered holly was administered to these patients without effect; all recovered quickly under quinine. If at the outset Chomel had given the powder of holly to his twenty-two patients it might have been concluded that it had cured the fever in nineteen out of twenty-two instances.



to wear a hat provided with a net such as that devised for the railroad employees in Italy, and to protect the ankles with gaiters, and the hands with gloves.

The medicinal measures consist in the use of quinine. There is no doubt of the great value of quinine as a prophylactic, but there is considerable difference of opinion as to the best method of administration. Good results have been reported from the use of daily doses of from grs. iiss.-iuss. (0.1-0.23 grm.), while others prefer giving larger doses with several days' intermission, grs. viiss.-xv. (0.5-1 grm.) every four to eight days. Experiments on a large scale carried out by the Italian society for the study of malaria shew that a daily portion of about grs. vi. (0.4 grm.) of quinine is better borne and gives more satisfactory results than larger intermittent doses—an observation which is also in accord with the conclusions of Mariani as to the cumulative action of the drug. Arsenic is of no value as a prophylactic.

W. S. THAYER.

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The literature on malaria is so extensive that a complete list of all the books and communications consulted in the preparation of this article would be unnecessarily long and confusing. Elaborate tables of references may be found in the treatises of MacLudava and Bignami in the *Twentieth Century Practice of Medicine*, and in that of Mannaberg in the English translation of Nothnagel's *Encyclopedia of Practical Medicine*. These two works are the most exhaustive in literature. It will be unnecessary to give special references to this valuable work of Daniels, Stephens, Christophers, and others appearing in the reports of the Malaria Committee of the Royal Society of London.

A mass of information of great value to the student of malaria is stored in the six volumes of the *Atti della Società per gli studi della malaria*, 8vo, Roma, vol. 1: 1899; vols. 2-6: 1901-5. The annual summaries of the work done under the auspices of this society by Professor Celli, communications of great importance, appear in various other publications, notably in the *Centralblatt für Bakteriologie*.

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W. S. T.

## THE PUBLIC PROPHYLAXIS OF MALARIA

By Prof. RONALD ROSS, C.B., F.R.S., LL.D., D.Sc., D.P.H.

THE modern prophylaxis of malaria is based upon the following leading facts ascertained since 1897: first, that the hæmocytozoa which cause the disease, when ingested by certain species of gnats of the sub-family Anopheline, undergo further development in them, and then after more than a week pass with the insects' salivary secretion into the blood of fresh human hosts; secondly, that these insects breed mostly in appropriate terrestrial waters in warm climates—thus explaining the old theorem that malarial fever, or paludism as it is often called, is connected with marshy areas. No valid evidence and arguments have yet been advanced in favour of the view that the disease can be produced in any other way. Hence a number of methods for checking or suppressing it can be suggested. If the parasites are assiduously destroyed by means of quinine in most of the patients in a locality, it follows that the mosquitoes will not become infected from them and will not therefore infect others, though they may be as numerous as before. Secondly, if healthy persons, such as Europeans newly arrived in the tropics, take care to live at a distance from infected people, such as native children (a large percentage of whom often harbour the parasites), then they are less likely to be bitten by mosquitoes which have infected themselves from the latter. Thirdly, precautions against the bites of mosquitoes, as by the careful use of mosquito-curtains and wire gauze screens to the windows, must largely reduce the chances of infection. Fourthly, destruction of the larvæ of the insects or obliteration of their breeding pools will have the same effect by reducing the number of carrying agents in a locality.

But a mere enumeration of these methods is not sufficient. All of them involve, for public prophylaxis at least, expenditure of labour and money, and also demand a knowledge, not only of this particular subject, but of public health matters in general. It would, of course, be best to employ all the methods simultaneously, but few malarious areas possess sufficient public funds for this, and the Health Officer is therefore generally compelled to consider carefully which of them he will adopt.

The first method, which is essentially that used for the prevention of many communicable diseases, namely, the detection, isolation, and treatment of the sick, is, in the case of malaria, difficult for large civil communities. To extirpate the parasites in a patient demands, let us



say, four months' assiduous cinchonisation ; and in many malarious towns a large percentage of the natives and nearly all the children may be infected. To deal with these would require a heavy annual expenditure for medical attendance and quinine, with examination of immigrants. The method is more promising for soldiers, Government servants, railway employees, and coolies, who can more easily be forced to submit to the treatment—which many rebel against. Public lectures on the subject, the publication of sanitary instructions, and the cheap sale of quinine form part of the campaign ; but practical sanitarians acquainted with the inertia of the public, even in civilised communities, will probably prefer other measures if practicable.

The second measure—the segregation of the healthy—is one which has long been used in India, where the Europeans generally live in separate cantonments. It protects only a section of the public. In places where it has not already been adopted, it will generally demand the building of a new station for Europeans. This will be costly, and the question will always arise whether the same amount of money could not have been better spent in protecting the whole public, European and native alike. Besides, complete segregation is almost always impracticable.

The third measure—mechanical protection from mosquito bites—is invaluable for private prophylaxis. A careful person may probably avoid over ninety per cent of the average number of mosquito bites, and thus reduce by the same amount his chances of being infected. All public buildings ought invariably to be protected by screening, and there is no reason why private houses should not be screened in British Colonies as they so frequently are in America. But the mass of the population will not easily be persuaded to spend the necessary money—at least in the tropics ; and public funds can scarcely be used for the purpose.

The fourth measure—the reduction of mosquitoes by drainage or other treatment of their breeding-waters—possesses the following advantages. It can be effected by the local authority, if necessary without the co-operation of the public—which is practically always difficult or impossible to obtain in connexion with sanitation on account of public ignorance of science. It does not demand expensive additions to private houses nor the prolonged use of any drug by private persons. It benefits, not a few individuals, but the whole community. It tends to diminish not only malaria, but other mosquito-borne diseases, and not only disease, but a general source of annoyance. The necessary measures are (*a*) permanent and (*b*) annual. The first consist of permanent works of drainage or filling up of pools, ponds, and marshes, the “training” or rectification of water-courses, the margins of lakes, and so on ; the second require the constant services of a sufficient sanitary staff for preventing the formation of small pools of rain-water and the accumulation of water in tubs, drains, gutters, and broken vessels (1). Such measures have the further advantage of improving the general sanitary condition of a town.

In comparing the merits of these methods, the Health Officer must

to consider which is likely to give the greatest amount of improvement to the public health for the sum of money at his disposal. For example, £1000 he may be able (1) to build a "segregated" bungalow for a single European family; or (2) to protect fifty houses with wire-gauze at an average cost of £20 per house (the gauze lasts only for a few years); (3) to abolish 200 breeding-pools at the average cost of £5 each. The balance of advantages will vary with local conditions. Generally, for isolated houses, screening is called for, and draining will cost more than it will be worth. On the other hand, for towns draining is likely to benefit the greatest number of persons for the least expenditure. For troops and officials segregation is always useful; and the detection and treatment of the sick must be urged whatever other methods are employed, because otherwise, even if local infection be absolutely abolished, a number of relapses will occur among old cases for years to come.

The policy of mosquito reduction is essentially that of drainage against malaria, which has been known since the time of the Romans, except that we now recognise with greater precision which kinds of waters are dangerous, namely, those which contain the larvæ. Doubt is often expressed as to whether local suppression of breeding will suffice to reduce mosquitoes because of their possible immigration from outside. Such hypotheses will not bear scrutiny. Mosquitoes are never uniformly diffused, but abound most in proximity to their breeding-places. Though a few may wander for considerable distances, the vast majority remain close to where they were born. The number of immigrants into an area of any size must always be small compared with the number of natives. To suppose that the mosquito population will remain the same after local suppression of breeding is equivalent to supposing that the human population of Britain would not be affected by abolishing the birth-rate. Every year during the hot weather nature tends to reduce mosquitoes by drying up the breeding-pools. Our object is merely to imitate nature in this procedure. Complete suppression of mosquitoes is perhaps always possible; but we may estimate, on grounds which cannot be discussed here, that a small reduction in their numbers is likely to produce after the lapse of sufficient time a great reduction in the local amount of malaria (2).

No exact method for enumerating the number of mosquitoes within a given area is known. Estimates of the amount of malaria, or of its decrease or increase, require great care in preparation. Poisson's formula could be used before generalising on ratios. For instance, if twenty-five out of fifty persons are found to be infected, the general ratio of infection (endemic index) is not fifty per cent, as many might assert, but would be something between thirty and seventy per cent.

During the last seven years anti-malaria campaigns have been conducted with encouraging results in many parts of the world. Perhaps the most decisive cases are those of Ismailia, and of Klang and Port Swettenham in the Federated Malay States. The first is a town of under 100 inhabitants, situated close to the Suez Canal and controlled by the



Suez Canal Company—the medical department of which has kept very exact statistics for many years. The number of cases of malaria rose from 300 in 1877 to 2250 in 1900. A campaign of drainage and treatment of old cases was commenced in 1902, with the following results:—

Years	1900	1901	1902	1903	1904	1905
Cases	2250	1990	1548	214	90	37

Nearly all the cases in 1904 and all of them in 1905 were cases of relapse among patients previously infected. The cost appears to have been about £1000 a year (3).

Klang and Port Swettenham are neighbouring settlements with a population of over 4000. Anti-malaria measures, mostly consisting of drainage, were commenced in 1901-2. The admissions for malarial fever into hospital for these towns were as follows:—

Years	1901	1902	1903	1904	1905
Cases	510	199	69	32	23

In the surrounding district the disease has increased. The cost was about £10,000 for permanent works, and about £400 for annual upkeep, in both towns combined. For them, as for Ismailia, the medical officers report that malaria has practically disappeared (4).

The Health Officer proposing such campaigns must expect to be put to considerable trouble, but should remember that the work is part of his duties. The persistence of much malaria in any town can only be looked upon as proof of sanitary maladministration.

For British readers the most accessible literature on the subject will be found in numerous articles in the *British Medical Journal* and the *Journal of Tropical Medicine* from 1899 onwards.

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R. R.

## BLACKWATER FEVER

By J. W. W. STEPHENS, M.D.

SYNONYMS.—*Hæmoglobinuric fever, Bilious remittent fever.*

**Definition.**—These and other alternative names have been applied to a fever, generally believed to be malarial in kind, which is accompanied by the presence of blood-pigment in the urine.

**Geographical Distribution.**—Its exact geographical distribution is not yet determined, for there is reason to believe it occurs in countries and districts in which it is not generally supposed to exist; *e.g.* it occurs in certain districts of Madras, as reported by Dr. Christophers and myself, where previously there was no published record of its existence. Broadly speaking, it is a disease of tropical or subtropical countries. It is perhaps best known in Africa, though even here we are not in a position as yet precisely to delimit it. It occurs certainly all along the coast of Africa, from the river Senegal to probably as far south as the Orange River, for it is well known in Damaraland. On the east coast of Africa it is found from British East Africa to as far south as Delagoa Bay. In the countries drained by the Niger, the Congo, and the Zambesi it exists. Cases have recently been reported from the upper reaches of the Blue and White Nile. It exists also in the countries bordering the coast line, such as Senegambia, Gambia, Sierra Leone, Gold Coast, Lagos, Cameroons, British and German East Africa, and Portuguese East Africa. In all these districts blackwater fever exists, but we have no means of accurately estimating its frequency in these regions, and any comparisons of this sort are most fallacious. For if, as is admitted, Europeans are chiefly attacked, the incidence in any locality will depend in part upon the extent of the white population, and no data exist for any real comparison; we shall see later other reasons for doubting the validity of such comparisons. In Algeria the brothers Sergent state that it is certainly less rare than is generally believed. They record 31 cases with 22 deaths in 2 years. In Egypt itself, so far as our knowledge goes, it does not exist. In Madagascar it has been described since 1851. It occurs also in Mauritius and Bourbon; with regard to Zanzibar no statement can be made. How far south in Africa it extends is not yet known. It almost certainly does not occur in Cape Colony.

With regard to the countries bordering the Mediterranean basin we have no very precise information, but we know of its existence in Palestine, Greece, Turkey, Italy (South), Sicily, and Sardinia. In Russia it has been described at Merv, though there is no reason to suppose that this represents its real distribution. Marchoux states that it exists along the banks of the Danube and in the Caucasus.

In *North America* it exists in the following states: Arkansas, Mississippi, Louisiana, Tennessee (?), Texas, Florida, Georgia, North Carolina, Alabama, South Carolina, Virginia. In *Central America*: in Nicaragua, Costa Rica, Venezuela. In the *West Indies*: in Cuba, Martinique, and Guadeloupe, in French, British, and Dutch (?) Guiana, in British Honduras. It occurs also in the Argentine Republic and Brazil, but precise data are wanting (it is rare, for instance, at S. Paulo (Lutz)). In *India*: in the Duars and Terai (Bengal), in Assam, in the Jeypore agency (Madras), in Canara district (Bombay). Certainly over large areas of India it is absent or very rare. Marchoux states that it exists in Burma. In *China* it has been recorded from Cochin China and Tonkin. It occurs in Java, especially at Tjilatjap, New Guinea (German); in the Federated Malay States and Strait Settlements a few cases occur annually. In Formosa it is not uncommon (personal communication), but it does not occur in Japan; a single case has been recorded in New Hebrides. Such a list in skeleton form is as much as we can give at present; we have not the necessary data for describing with any accuracy or completeness its geographical distribution, nor can we do more than state very indefinitely that it is common in one place, rare in another.

Although blackwater fever never originates in non-malarial countries, the clinical manifestations of the infection, as of other forms of malaria, may shew themselves in non-malarial countries, and shew themselves there perhaps for the first time. Thus, attacks of blackwater fever may occur in England many months after the patient has left Equatorial Africa, and may even prove fatal. It would seem, however, that the liability to such attacks diminishes with lapse of time, and practically ceases after a prolonged residence in this country.

**Causation.**—In considering the vexed question of the etiology of this disease it will be well to exclude hypotheses rigidly, and to ascertain as far as possible known facts. Further, it seems to me of great importance, in making comparisons between the prevalence of blackwater fever in various countries, to be certain that as far as possible similar conditions are being compared. Let us assume for the moment that blackwater fever is malarial in origin. How then is it possible to explain its absence in Italy as a whole and its occurrence in Sicily, both of which are malarial countries? Whatever be the answer, a closer inspection of this objection shews that, according to Celli, malaria in Sicily has a mortality of 7-8 per 10,000; while over large tracts of Italy it does not reach 1 per 10,000, and it is only in the south, where the value is 9, that we again find blackwater fever. It will be well to remember that in North Italy malaria is in a sense a mild disease, but that in tropical Africa it is an intensely severe disease. Climate, whatever this implies, totally changes the aspect of malaria, as is evident to everybody who has seen patients in Africa and patients—possibly the same ones—in hospital in England. We have to take account of another difference which makes comparisons almost impossible. Assuming, again, that the disease is

malarial, then we have to consider the population with which we are dealing—first, whether we are referring to the native inhabitants of a country, be they white or black, or to immigrants, previously uninfected with malaria, into a malarial district. It is true, for example, that among adult negroes malaria is uncommon or, at any rate, it affects them in a manner quite different from that in which Europeans are affected. Adult negroes enjoy an undoubted immunity, while to the European in Africa malaria is a deadly scourge. It is evident, therefore, that comparisons between an immigrant and resident population, or European and negro population, in the matter of malaria is impossible, the two things differ so much. Again, we have to consider the conditions under which the population lives. Malaria is not a disease of towns, and there is hardly more malaria in Bombay, Madras, or Calcutta than in Rome. It is different, however, in the malarial regions of the tropics. The great majority of Europeans live under conditions of continued malarial infection owing to the propinquity of native dwellings, which swarm with anophelines infected with malaria by the native children. There is not the separate cantonment of European and native population which is so characteristic a feature of Indian settlements. Consequently, apart from other reasons, it is uncommon—with exceptions to be mentioned later—to find Europeans in India so “saturated” with malaria as is unfortunately the case with the European in Africa, especially among those who live under what are nothing less than primitive conditions of civilisation and comfort. There are additional factors which make it impossible to draw scientific comparisons between the malaria of different regions. Among these is the particular variety of parasite that causes the infection. In the case of Europeans in India the fever is mainly due to the simple tertian parasite; in West Africa, on the contrary, it is exceptional to find an infection with this parasite, the predominating species being the malignant tertian. We would finally mention the possibility that an infection transmitted by a certain species of anopheline may be more severe than one transmitted by another species, but of this we have no evidence.

Although, then, there is need of discrimination in the use of such a word as malaria, which may imply diverse conditions in diverse places, we may now turn to the question, What is the evidence for regarding blackwater fever as malarial? and indeed this is the sole question we have to determine, for no other opinion, and there are several, has any basis of fact to support it. For example, all investigators have been struck with the apparent similarity of this disease to haemoglobinuria in cattle, the parasite of which is well known; but all the evidence is conclusive that such a parasite as piroplasma does not exist in blackwater fever, and that the similarity is apparent only. The question of the etiology of blackwater fever, therefore, resolves itself into this—either it is malarial in origin, or it is due to causes about which, up to the present, we know nothing.

What then is the evidence in favour of the malarial origin of blackwater fever? (1) There is no case on record of blackwater fever having

attacked a person who has not previously, and most frequently only a short time previously, suffered from malaria. (2) The evidence is overwhelming—and I know of no competent author who has ever denied it—that blackwater fever is met with most frequently among those who have suffered for longer or shorter periods from repeated attacks of malaria. (3) In confirmation of this is the evidence furnished by the increased susceptibility to attack with the increased duration of residence of Europeans in tropical regions. Thus, Béranger-Féraud (2) gives the following data concerning the numbers attacked in consecutive years. First year, 5·4 per cent; second year, 22·5 per cent; third year, 42·5 per cent; fourth year, 20 per cent; fifth year, 4·8 per cent. Similar figures have been compiled by other observers. The facts are not denied. The interpretation is open to question, but it is, I think, good evidence that blackwater fever is not a disease due to a special parasite, protozoan or bacterial, otherwise it would not have this peculiar time distribution. The fall in the fourth and fifth years is explicable by the assumption that those who survive tropical service up to that date have proved themselves to possess resistance to malaria to which others have earlier succumbed. (4) The tropical regions of Africa are admittedly among the most malarial in the world, yet death from malaria simply is comparatively uncommon, death from blackwater fever very common (31). The true explanation of this, I believe, is not that tropical Africa is not intensely malarial, but that this intensity of malaria displays itself in blackwater fever. Thus, Doering observed 129 cases of malaria with 1 death, *i.e.* a mortality of 0·77 per cent, and 40 cases of blackwater fever with 5 deaths, *i.e.* a mortality of 12·5 per cent. This, which is below the average mortality for blackwater fever, is sixteen times as great as that of malaria. (5) If blackwater fever be malarial in nature, then those who escape malarial attacks by any means, whether by efficient use of mosquito-nets or by quinine prophylaxis, should escape blackwater fever. That this is so the following data shew:—A. Plehn (24) carried out in the Cameroons comparisons between those who regularly took quinine and those who did not. During the period 1897-99 observations were made on two series of colonists. The figures in the first row are of those who did not take quinine, in the second row of those who systematically did ( $7\frac{1}{2}$  grains every fifth day):—

Attacks of Malaria.	Interval between Attacks in Months.	Blackwater Attacks.	Interval between the Attacks in Months.	Deaths from Blackwater Fever.
287	2	31	18·5	10% (about)
90	5	6	74·0	0

The evidence hitherto cited is of a general kind. I believe the data given above to be correct; the inference to be drawn from them will

however, depend on personal opinion. To my mind they are evidence of the malarial nature of blackwater fever, but others may interpret them differently. One of the commonest objections to the malarial view of blackwater fever is that the distribution of malaria and blackwater is not the same. I have already pointed out the vagueness of the term malaria, but I think the following statement, viz. "that the distribution of intense malaria and blackwater fever corresponds very closely," is not far from the truth. We shall next consider evidence of a special kind.

(b) It has been urged against the malarial origin of blackwater fever that malarial parasites are seldom found, and that when present their number bears no relation to the severity of the attack. We shall see later that this statement is not strictly accurate, but for the present we may regard it as in the main true. It is also true, however, that it is possible to get typical attacks of malaria in which it is almost impossible to detect parasites. The most frequent, but not the only cause of such a condition is the previous administration of quinine. In such cases Dr Christophers and I have shewn that there are two tests by which a quite recent malarial infection can be detected: (a) the presence of pigmented large mononuclear leucocytes, (b) the increase in the percentage of large mononuclear leucocytes—over 20 per cent. By the application of these tests to a series of sixteen cases of blackwater fever we found clear evidence of malaria in 93·8 per cent of cases, while parasites were found only in 12·5 per cent of cases. In a control series of cases, selected from those constantly liable to malarial infection, the evidence of such infection, based on the presence of pigment or parasites, existed in less than 10 per cent and some of these had high temperatures when examined; while including even those who had only a slight increase of mononuclears the percentage was only 20 per cent. It is, therefore, an error to suppose that any series of persons in the tropics would shew similar evidence of malarial infection to that which the blackwater patients shewed. Not only is this not so, but in the above control experiments those examined were not an average healthy community, but were especially selected as being liable to infection. But the evidence in favour of the malarial origin of blackwater fever is even stronger than this. As stated above, it is not strictly true that parasites are seldom found in cases of blackwater fever.

(c) Thus, I tabulated a series of ninety-five cases (31) in which blood examinations had been made by competent observers and found that the detection of parasites depended almost entirely upon the time when the blood examination was made. In cases where the blood was examined on the day before the onset of haemoglobinuria, parasites were found in 95·6 per cent of cases, on the day of the haemoglobinuria in 61·9 per cent of cases, on the day after the haemoglobinuria in 17·1 per cent of cases. The conclusion seems inevitable that we are dealing here with cases of malaria. A denial of this would seem to me to be equivalent to denying the causal significance of malarial parasites in an equivalent number (95·6 per cent) of ordinary malarial cases. We do not assert



that parasites will be found in every case of blackwater fever, for there is undoubtedly a condition of malaria in which, though fever persists in spite of regular doses of quinine, yet no parasites occur in the peripheral blood. Before we consider why parasites are found only in a certain number of cases of blackwater fever when examined the day after the onset, it will be necessary to discuss another factor in the causation of this fever.

Without entering into the history of this part of the subject it will be sufficient to state that Tomaselli, in Sicily, first published a series of cases of hæmoglobinuria in which he considered that this symptom of the fever was due to quinine, and indeed that these cases were to be regarded as cases of quinine intoxication. This possibility has been vehemently denied, but cases are now on record in which the facts admit of no denial. Patients who have themselves known that quinine did induce in them the passing of hæmoglobinuric urine have voluntarily submitted themselves to experiment, and it has been conclusively shown that in such cases quinine can and does induce hæmoglobinuria. It is, indeed, a matter of common experience that quinine, as a rule, has no such action; but to deny the possibility of its provoking hæmoglobinuria is no longer justifiable, for such cases are fortunately on record—having been observed in hospital. Such cases of production of experimental hæmoglobinuria by quinine are within the knowledge of most medical men in tropical Africa. It may be regarded as established that quinine can produce hæmoglobinuria; what, then, is its relation to blackwater fever? It may be stated that some observers consider that clinically quinine hæmoglobinuria can be distinguished from blackwater fever, and base the distinction mainly on the greater severity of the symptoms in the latter, *e.g.* extreme collapse, stupor, and the high temperature; but we doubt whether the distinction is a real one, and believe that all stages between the mildest attacks and the severest attacks occur. It is difficult to prove the opinion, now widely held, that quinine is the determining cause in the onset of blackwater fever [for literature *vide* under (31)], but the most convincing proof is the observation of an actual case when in a patient who may be progressing favourably after the initial attack, suddenly hæmoglobinuria again supervenes, the only changed condition having been the administration of quinine a few hours previously. That quinine is the most frequent cause of blackwater fever in those suffering from malaria is the opinion of many who have studied the disease carefully. There are, of course, many obvious objections to such a view. Thus (1) quinine produces, we will suppose, a blackwater attack on one day, but there is no certainty that it will do so on the following day—indeed the probability is in the other direction; (2) thousands of patients are treated daily with quinine, but no blackwater fever arises; therefore, it is said, it is absurd to assert that quinine is the cause of blackwater fever. Objections of this kind are, I consider, deprived of any force they might possess by the observation already mentioned, that quinine has been proved experimentally to be able to give rise to hæmoglobinuria. This



experience outweighs all conjectural arguments.<sup>1</sup> There are undoubtedly cases of blackwater fever in which the influence of quinine as the exciting cause can be excluded; in my opinion they are few in number, and they cannot suffice to contradict positive experimental evidence. Not to prolong the discussion of the etiology further, we may sum up by declaring that we believe the facts to be as above stated; the interpretation of them is a matter of opinion. I regard the condition of blood necessary for the development of blackwater fever, *i.e.* of an acute hæmolysis, as determined by exposure to malarial attacks of a greater or less frequency; that in the majority of cases, if not in all, the *initial* attack is associated with the definite occurrence of parasites in the blood, and that under such conditions quinine, not necessarily in large doses, is able to induce an acute destruction of blood-cells. This factor, *viz.* the quinine, and no doubt to a great extent also the hæmolysis itself, is the reason why parasites disappear so rapidly during an attack; so that commonly on the day subsequent to the attack none can be found. While then in the main the broad etiological factors of blackwater fever are, I believe, settled, yet it must be freely admitted that with regard to more exact pathological details we are still in the dark. It is possible, for example, that the hæmolysis takes place largely in the kidneys—that, as Plehn (24), for instance, holds, a kidney lesion is also one of the essential factors.

In this connexion attention should be called to Marchoux's important observation, that during the hæmoglobinuria quinine cannot be detected in the urine, but that on the cessation of hæmoglobinuria it reappears. The obvious explanation may, of course, not be the true one. Bearing on the action of quinine the observation of Poch is also of considerable importance: In a patient who some time previously had had an attack of blackwater fever, the red cells had reached a value of 6,000,000. On administering 15 grains of quinine a diminution of 340,000 occurred without any other symptoms. There are also observations on record in which quinine has been administered on several occasions with the production of hæmoglobinuria, while on a subsequent occasion albuminuria and a high-coloured urine have resulted.

The etiology of blackwater fever may be summed up by saying that it is malarial in nature, *i.e.* it can only occur in those who are either suffering from, or have quite recently become infected with, malaria, and that the onset of the disease is induced most commonly, though not invariably, by quinine.

**Morbid Anatomy.**—The following changes observed in a typical case of blackwater fever may be taken as representing those usually found.

**Spleen.**—Malarial pigment occurred in the cells of the splenic reticulum, and also in macrophages and in large mononuclear leucocytes. Besides the melanin a varying amount of yellow pigment (hæmosiderin)

<sup>1</sup> Those who have so long opposed the view that quinine is the cause of blackwater fever now advance the hypothesis that quinine is simply the immediate determining factor in bringing some unknown parasite into action.

occurs. Parasites are generally absent, though they may be found here when absent in the blood during life.

*Liver.*—(a) Small necrotic foci, situated laterally to the intralobular vein. These areas consist of necrotic liver-tissue. (b) Small thrombi in the sublobular veins. The thrombi contain a few pigmented cells. (c) Pigment (melanin) in the endothelium in spherical clusters, hæmosiderin in the liver-cells, and pigmented leucocytes in the vessels.

*Kidneys.*—There is no indication of any acute inflammatory process, but the epithelium of the convoluted tubules shews much degeneration, and the lumen is filled with a granular mass; the straight and collecting tubules are also filled with shed epithelium and masses of granules. No melanin occurred in the kidneys.

*Red Marrow.*—Melanin occurs in the capillary endothelium, in large branched cells, and in leucocytes.

*Brain.*—In some instances sporulating parasites have been found here, though there was little evidence of malarial infection elsewhere. Frequently, however, no pigment can be found here.

**Symptoms.**—A characteristic attack of hæmoglobinuric fever is usually ushered in by an initial stage of shivering, which may increase into a series of severe rigors lasting for some hours. There is a sense of numbness in the extremities, intense pain in the loins, and general malaise.

The temperature rapidly rises to 103° F. or thereabouts, mounting at a later period to 105° F., or even higher; and dark-coloured urine is sooner or later passed from the bladder. Frequent retching, attended in nearly all severe cases with bilious vomiting, is a distressing symptom which is apt to exhaust the patient—this persistent vomiting of green bile being almost invariably present in cases tending to a fatal termination. Tympanites is a common and distressing symptom. At an early stage a more or less intense jaundice becomes rapidly established, the conjunctivæ and the skin over the entire surface of the body becoming of a bright yellow colour. The considerable pain over the region of the kidneys, which not unfrequently gives rise to much complaint, may be due to some congestion of those organs; and actual nephritis is occasionally set up as the result of the great elimination of hæmoglobin, but is not usually found after death. Frequently also there is much pain in the region of the liver and spleen, and these organs are enlarged. The pit of the stomach may also be sensitive to pressure.

The fever, which becomes somewhat marked at the very beginning of the paroxysm, may be remittent or almost continuous in course. Usually, however, after a longer or shorter interval the temperature drops somewhat, and the patient falls into a profuse perspiration. If so, all the various painful symptoms tend to abate; but an intense feeling of weakness remains. Coincidentally with the subsidence of the fever the urine loses its dark colour, reverting after a time to its normal condition. The paroxysm may now cease as suddenly as it began, but the temperature may rise again; rigors and pains in the loins and over the liver return, while the urine once more becomes red or almost black.

In the severer class of cases the symptoms persist without any apparent intermission, the urine becomes more and more scanty, and eventually may be entirely suppressed; in these circumstances a fatal termination usually follows after no long interval. Death may be ushered in with a convulsion, or it may result from syncope or collapse, or again death may result from hyperpyrexia.

The course of events is not, however, always like that depicted. Not uncommonly the patient does not know that he is ill until he passes "blackwater." He may, perhaps, have had some slight febrile rise which is often quite neglected, the icterus may be hardly appreciable, and it is only the dread of "blackwater" that induces the patient to take to his bed. Between the mildest attack of this sort and the severe and frequently fatal attack depicted above we may have all gradations. The more severe forms may be accompanied by bloody diarrhoea. Hiccup is often a distressing feature, and in cases that shew a diminished urinary excretion is of unfavourable import. Somnolence in severe cases is likewise unfavourable. Vomiting, when persistent, may lead to a distressing state of exhaustion of the patient, terminated only by death, on the other hand it may be almost entirely absent or only slight. Marked enlargement of the submaxillary glands is a somewhat rare complication. Pain in micturition is not uncommon.

On the day after the paroxysm the temperature may fall to normal, accompanied by profuse sweating. The patient, who at first was in a state of stupor, now regains his senses and experiences a sense of comfort. Sleep may ensue, and the patient may make a good recovery. Should a relapse ensue the symptoms are repeated, sometimes with greater, sometimes with less intensity; in the former case the pulse becomes feeble, the temperature is generally raised, weakness increases, there is mental cloudiness, icterus becomes intense, fæces and urine are passed involuntarily, hiccup is constant, and death soon occurs. In milder cases vomiting, want of sleep, restlessness, may for a time make the issue doubtful, but the symptoms gradually subside, the urine clears, the patient gradually gains strength, takes a little solid food, then gets up from bed, and eventually recovers.

The *blood* shews but little evidence of the intense hæmolysis that may have occurred. A careful examination would not enable one to say more than that the corpuscles displayed some amount of anæmia. To the naked eye the blood is "thin" in appearance, and has lost its stickiness, so that in making a film the blood adheres to the slide with some difficulty. Often, too, the serum can be seen to be deeply yellow, an appearance more readily appreciated by allowing a drop to coagulate in a capillary pipette. Not unfrequently the serum shews no trace of hæmoglobin, although the hæmoglobinuria may be actually increasing. Hæmoglobinæmia does, however, occur.

In stained preparations normoblasts may occur, and especially some time after an attack, polychromasia of the red cell and basophil punctation. Both these appearances have been considered to be of

some diagnostic importance, and if well-marked, to make a further administration of quinine dangerous. This point, however, requires further examination.

*Parasites.*—We have already dealt with this question. As a rule the observer will be struck with the negative results of his examinations, but provided the blood examination is made early enough (before the attack!) parasites will nearly always be found.

*Pigmented Leucocytes.*—Those who have made many thousands of blood examinations in malaria know how often it is difficult to find these except by long search. In blackwater fever search through a couple of well-made films will nearly always reveal a pigmented mononuclear leucocyte; occasionally, indeed, as in malaria, they are abundant. When absent in the blood they may be found in abundance in the spleen (post-mortem).

*Leucocyte Changes.*—Frequently there is, as in malaria, an intense leucocytosis accompanying the rigor. Later, especially when the temperature falls, there is leucopenia and an increased percentage of large mononuclear leucocytes. The importance of this change, coupled with the presence of pigmented leucocytes, has already been discussed. During the leucocytosis this change may be masked by the increase of polymorphonuclear leucocytes to as much as 90 per cent.

The *urine* is often faintly alkaline in reaction and of a specific gravity below the normal. In colour, that which is first passed during a paroxysm is of a deep reddish or blackish-red tint, the amount of the contained pigment being large; while when the attack is less severe, or is passing off, it may exhibit all variations of hue between that of port wine and of dark sherry. The total amount of urine passed is frequently increased, and micturition may be frequent; on the other hand diminution may occur, and this may progress towards practically complete anuria. The amount of albumin in dark urines may be so great that on boiling the contents of the test-tube set solid. Exact analyses of the proteid constituents—certainly to a great extent globulin—are still wanting. A urine that looks dark may often be cleared by centrifugalisation, when a spectroscopic examination may shew that no hæmoglobin is present. The sediment in these cases consists of a granular yellowish material varying in size from  $1\ \mu$  to  $7\ \mu$ , which is supposed to be altered blood, and, indeed, this sediment is a characteristic feature of the urine in all severe cases. In this sediment may be found a few minute reddish crystals (? bilirubin).

Red blood-corpuscles are for the most part conspicuous by their absence. In certain instances, however, the hæmoglobinuria is accompanied by a true hæmaturia.

In the urine spectroscopically examined in a thin layer, or diluted to the requisite degree, the absorption-bands characteristic of hæmoglobin present themselves. Very frequently the presence of a third band, situated between the C and D lines, affords evidence of the conversion of the pigment into methæmoglobin, and it remains to be seen whether both

hæmoglobin and methæmoglobin are present together. Almost invariably urobilin is present in the urine. For its detection it is best first to precipitate the hæmoglobin-pigments, but this is not always necessary. Bile pigment in the urine is very uncommon. In certain cases, however, bile pigments may appear in the urine with the onset of the usual symptoms, while hæmoglobin is still absent, and it is only later that there is true hæmoglobinuria.

**Diagnosis.** - Probably the only disease for which hæmoglobinuric fever is likely to be mistaken is yellow fever. The invasion of both diseases is marked by somewhat similar symptoms; but, after the first few hours at any rate, no great difficulty is likely to be found in diagnosing the true nature of the illness.

The history of the case will be of great assistance. Almost invariably, if careful interrogation be made, there will be a history of repeated attacks of fever and an attempt to check these by quinine. The enlargement of the spleen points to present or past malarial infection. The character of the vomit is quite different in the two affections. In blackwater fever in severe cases pure green bile is vomited. In yellow fever the vomit is dark brown or black. The urine, however, affords the most convincing distinction. In blackwater fever the hæmoglobinuria varies from a light red to an almost black colour, and it is only rarely that red cells are found microscopically. In yellow fever there may, on the contrary, be a true hæmaturia, but this is rare. The colour of the jaundice in the two diseases is also different, in yellow fever it is of a box-wood colour, while in blackwater fever it is citron-yellow (*vide* p. 340).

Pathologically the points of difference between these two diseases are even more marked; after death from hæmoglobinuric fever the stomach shews no special alteration, except that its internal surface may appear pale and anæmic; but in yellow fever the mucous membrane is for the most part soft and intensely injected, and the cavity of the organ usually contains blackened and disintegrated blood. The skin is of a variable yellow colour, and violet or dark red patches occur in parts. Small hæmorrhages are also found. These are especially noticeable internally on the serous membranes and mucosæ, and also occur on the membranes of the brain. In yellow fever the spleen is soft, but not enlarged, the liver is more or less fatty and yellow in colour, and contains very little blood. In hæmoglobinuric fever, on the other hand, enlargement of the spleen is often marked, and the liver is hyperæmic and contains hæmoglobin and often melanin. The possibility of confusion with acute yellow atrophy of the liver and phosphorus and other forms of poisoning should be borne in mind.

**Treatment.**—If the view that we have here put forward, viz the causal influence of malarial infection followed by the administration of quinine be true, then the difficult question arises as to the justification of administering quinine even if parasites be found. There can be little doubt, I think, that on the whole practical experience is against the administration of quinine, whatever be our view as to the nature of the



disease. Certainly a physician would do well by microscopic examination to ascertain what actually is the condition of the blood, and to refrain from quinine unless the parasite infection be a massive one. If it be true that the patient is infected with malaria, then, in order to combat this, quinine should be commenced during convalescence in small doses, 1 or 2 grains at a time, and the effect carefully watched. If well borne, and the fever does not threaten severely, this may be continued daily for some weeks, and eventually 5- and 10-grain doses given, and if no untoward accident occur this must be persisted in for months or a year, in order that the system may be entirely freed from the malarial infection. The bowels must be freely opened by drugs—of which calomel and jalap, either separately or combined, are the most generally useful—aided by enemata; and if severe vomiting be present treatment must be especially directed to this symptom. If ice can be obtained the patient should be allowed to suck it continually; and small doses of brandy or champagne will probably be retained even when nothing more nutritious can be given by the mouth. Hearsey records twenty-one consecutive cases without a death treated by a mixture containing bicarbonate of soda (10 grains) and perchloride of mercury (℥xxx.) in each dose. This is given every two hours on the first day. Vomiting he controls by  $\frac{1}{2}$  grain of morphine hypodermically. Acid drinks are prohibited. Doering has had good results in the alleviation of vomiting by the use of Karlsbad salts (a teaspoonful) in water, repeating the dose if vomited. He attributes the good results to the relaxation of the bowels. Boracic acid is used by others, but beyond the symptomatic treatment there is no drug that can be said to possess specific value.

In severe cases it will be necessary to resort to nutrient enemata, and, if the temperature should fall below normal, hot-water bottles should be placed in the bed. Resort may also be had to intravenous injections of normal saline solution, which can be made by dissolving a dram of common salt in a pint of water, boiling the mixture to sterilise it, and then allowing it to cool to a temperature of 105° F. prior to use: experience has shewn that better results may be thus obtained than if a lower temperature be employed.

*Prophylaxis.*—If the view we have taken of the malarial nature of blackwater fever be correct, it follows that a person who has *never* suffered from malaria will never suffer from blackwater fever. The prophylaxis of blackwater fever, we believe, is identical with that of malaria. It is possible for every one who will exercise the necessary intelligence and care to escape malaria completely. There are many, however, who will not be at the trouble of protecting themselves by the proper use of a mosquito-net and simple precautions in regard to clothing. The only alternative for such persons is to submit to a stringent quinine prophylaxis. This may be carried out in several ways; among the best is a dose of 15 (or 10) grains of quinine every ninth and tenth days. If a person is already suffering from malaria the physician should on no account rest satisfied until, by prolonged and adequate treatment with

quinine, the infection has been entirely eradicated. The condition of "small fevers," more or less continuous, with inadequate quinine administration is, I consider, especially dangerous, and it is this condition that the physician should do his utmost to combat by adequate doses of quinine. In such a method of prophylaxis there is no danger of hæmoglobinuria, it is the combination of inadequate amounts of quinine and a continuance of slight fevers from time to time that seems especially to favour the onset of blackwater fever.

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#### TICK FEVER

By PHILIP H. ROSS, M.R.C.S.

**Definition.**—A specific fever caused by the presence in the blood of a spirochæta, and characterised by one or more febrile attacks of varying duration. The spirochæta is conveyed by the bite of a tick, the *Hemodorus moubata* Murray (*vide* p. 194). The disease may also be conveyed by inoculation with infected blood.



**Etiology.**—Tick fever was first described by Dr. Livingstone as occurring in the basin of the Zambesi. More recently a disease attributed to the bite of an ornithodoros has been noticed in Uganda, in German East Africa, in Central Africa, and in the Congo Free State. The disease probably passed under different names in the various countries, but it was always attributed to the bite of a tick which infested old camping-grounds along the caravan routes. In 1903 Marchoux and Salimbeni described the spirillosis of fowls, common in Rio de Janeiro, and shewed not only that the disease was due to the presence of a spirochæta in the blood, but also that the spirochæta was conveyed by a tick (*Argas miniatus*), and that this tick, after biting an infected fowl, remained infective for as long as five months. Following this work with the spirillosis of fowls, P. H. Ross and A. D. Milne in Uganda, in a series of cases of fever, ascribed by the patients to the bite of a tick (*Ornithodoros moubata*), demonstrated the presence of a spirochæta in every case. Drs. Dutton and Todd in the Congo then shewed by experiment that the spirochætæ were conveyed to a healthy subject by the bite of an ornithodoros which had fed on a patient suffering from tick fever, and that the larvæ, hatched out from eggs laid by an infected tick, could convey the infection at their first feed. Borrel and Marchoux, working with the spirillosis of fowls, shewed that the spirochætæ actually developed in the interior of the argas, but that the development, which took place readily at 35° C., did not do so at 18°-20° C. Theiler, in South Africa, in the case of spirillosis of cattle, conveyed by the *Rhipicephalus decoloratus*, has shewn that there is hereditary transmission of infection from parent tick to offspring through the egg.

It seems, then, that in tick fever the tick may be infected in two ways. It may either have fed on a person suffering from the disease or it may be the offspring of an infected tick. For the development of the infection in the tick, from the analogy of the parasite of fowls, a high and fairly equable temperature is probably required. In support of this it may be stated that in the high lands of East Africa, where the nights are cold, infection-experiments with ticks brought from Uganda have always failed, although these ticks were fed in East Africa on animals whose blood was swarming with spirochætæ.

**Geographical Distribution.**—The disease has now been recognised by the identification of the tick and the finding of the parasite in Uganda, the Congo Free State, in Angola, and in German East Africa. In the latter country, the disease occurs not only round Lake Victoria in the regions adjoining Uganda, but also on the coast line at Dar-es-Salaam. Mesnil states that the disease in the Zambesi basin has also been identified as due to the same parasite. In the high lands of British East Africa, although for many years in communication with Uganda by caravan, the disease has not been found except in imported cases. In the light of the work of Borrel and Marchoux it seems probable that the disease will be found to be practically confined to hot and moist areas.

Drs. Dutton and Todd are of opinion that the spirochæta of tick fever



Chart I. TICK FEVER IN A NATIVE

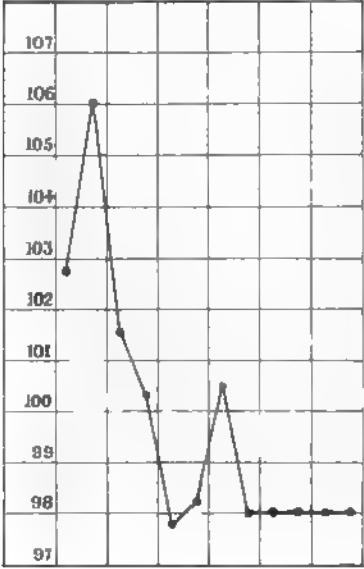


Chart II. TICK FEVER IN

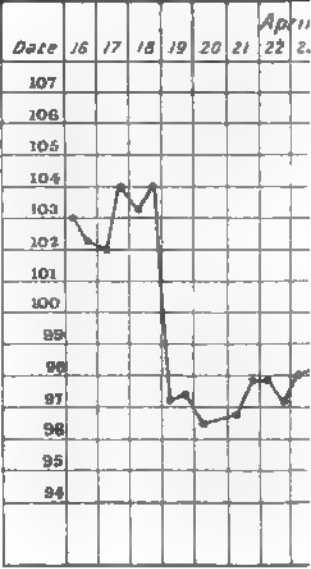
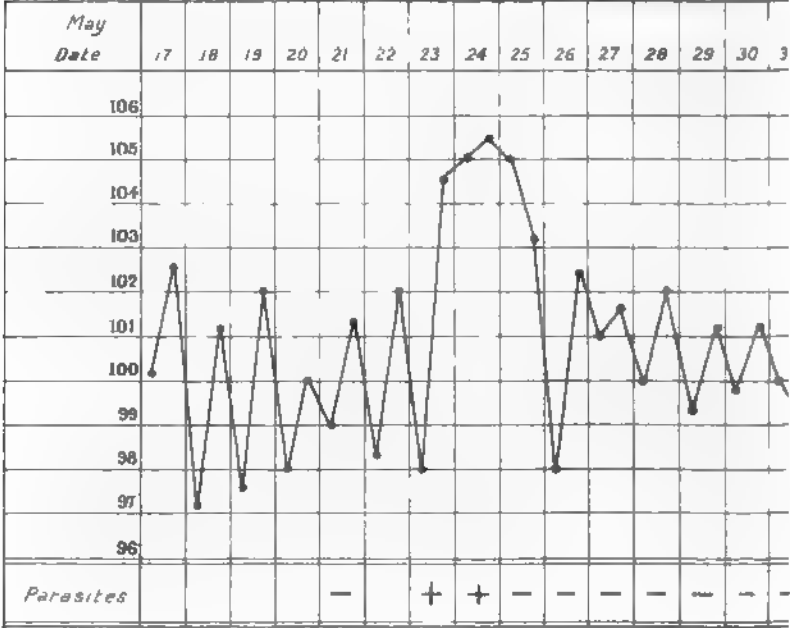


Chart III. TICK FEVER IN A MONKEY

Monkey (*Cercopithecus*)



the *S. obermeieri*, and that the disease is therefore the same as the relapsing fever of Europe. It is too early yet for the question to be decided. In favour of this view is the somewhat similar course of the disease in Europeans. But, on the other hand, the experiments of Henslow and of Major Lamb with monkeys (*Cercocebus fuliginosus* and *Macacus radiatus*) shewed that the inoculation of these animals with blood from a case of relapsing fever only produces one paroxysm of fever, whereas two species of cercopithecus and a cynocephalus, when inoculated from a tick fever patient, suffer from numerous relapses. (For description of Spirochæta see p. 46.)

Dr. Nuttall some years ago suggested that relapsing fever was conveyed by bed-bugs, and Schaudinn has lately found that the *S. obermeieri* does undergo development in the cimex.

**Post-Mortem Appearances.**—There is nothing distinctive to be seen post-mortem. There may be slight swelling of the liver and spleen, and a few petechiæ in the lung. Smears made from lung and liver shew large numbers of spirochætæ.

**The Incubation-period** is probably from three to eight days. The period varies between these limits when the disease is inoculated into a monkey. Natives sometimes give the period as one day; but the tick is a night-biter, living by day in the thatch and cracks in old huts and coming out at night for food. Such a short period as one day is probably only the interval since the patient last noticed that he had been bitten. The bite of the tick has varying local effects; on some people it leaves little or no mark, on others it may raise a red lump the size of a pea.

**Symptoms.**—The disease runs a different course in the European and the native, and as the symptoms vary accordingly, it would seem better to describe each separately.

In the native the chief symptoms are fever ( $103^{\circ}$ - $105^{\circ}$  F.), headache, stiffness in the trunk or limbs, and sometimes, but not always, vomiting. There may also be diarrhœa and cough, but these latter symptoms are not so constant as those before mentioned. The skin is hot and dry, the conjunctivæ are suffused, the tongue furred, and the respiration and pulse rates are both quickened. In some cases there is tenderness on pressure over the spleen, but neither the liver nor spleen are enlarged except by some previous cause such as malaria. The temperature remains elevated for from twenty-four to forty-eight hours with a slight morning remission. It then falls by crisis and either remains normal or subnormal, or may shew a slight rise on the following day. The symptoms disappear with the crisis, and the patient rapidly recovers. Relapses are very rare in the native. When they do occur, after an apyrexial interval of from one or two days to a week, the temperature rises and there is a recrudescence of all the symptoms. The relapse is usually of shorter duration than the initial attack, and the symptoms may be less severe; in rare cases there is a recurrence of the headache without either

rise of temperature or vomiting, but with the reappearance of parasites in the blood.

In the European the disease runs a very different course, and is more severe. There is at first a feeling of malaise, and if the patient is now seen, the temperature will be found to be slightly above normal. In a few hours all the symptoms will have developed. The temperature rises to  $104^{\circ}$  to  $105^{\circ}$  F., there is the most intense headache and obstinate vomiting first of food and then of bile. There are also pains in the trunk or limbs. In some cases there is diarrhoea, the stools having a dysenteric appearance, sometimes even being streaked with blood. The temperature remains high for from one to three days, shewing morning remissions. The temperature then falls by crisis to normal and all the symptoms disappear, leaving the patient feeling at ease but weak. After an interval, which may be as short as one day or as long as three weeks, there is a recrudescence of the fever and reappearance of the other symptoms; the patient has his first relapse. These pyrexial and apyrexial periods succeed one another until the disease may have been as many as eleven relapses; as a rule there are five or six. The symptoms are usually as severe in the relapses as in the initial attack and the fever is as high, but there is a tendency for the pyrexial periods to become shorter and for the apyrexial periods to become longer. There is the greatest variation in the course of the disease in different patients. The febrile period may vary in length between one and three days, and the intervals between one and eight days. But the main features of the disease are the same, the fever, the vomiting, the pains, and the vomiting all recurring together at irregular intervals. When the last relapse is finished the patient will be found to have lost a great deal of weight, and he may be so weak that he can hardly get up. He now passes into a slow but usually uninterrupted convalescence. It must be remembered that relapses may occur in temperate climates many months or more after the patient has left the country of infection.

Death is very rare. When it is going to occur the temperature falls to below normal without there being any improvement in the condition. The patient becomes unconscious and dies in a comatose state.

*Examination of the Blood.*—The parasites are usually so scanty in the peripheral blood, and so difficult to see, that it is useless to examine ordinary blood preparations. Blood-smears should be made and stained either by some modification of Romanovsky's method or by gentian aniline. The former method has the advantage of allowing the observer to look for malarial parasites at the same time. An oil-immersion lens should be used. Even in clinically well-marked cases it may take hours of searching to find one parasite. Sometimes nothing may be found during an attack, yet parasites may be found during a relapse. When found a single parasite is seen lying between the blood-cells in a characteristic shape, shewing from two to six undulations in its length. The schizont is from  $15\ \mu$  to  $45\ \mu$  long, with sharply pointed ends. It stains

niform blue with Leishman's stain, and shews no sign of structure nor chromatin.

There is a marked leucocytosis, and a differential count shews that polymorphonuclear leucocytes are increased relatively to the lymphocytes. The large mononuclear leucocyte count may be high, but in malarial countries it is practically impossible to exclude recent malaria, which would account for an increase in this element of the blood.

*Sequels.*—As a rule recovery is uninterrupted, but in some cases iritis occurs. As in syphilis, this usually affects one eye before the other.

*Diagnosis.*—The disease with which tick fever is most frequently confused, and from which it is most difficult to make a differential diagnosis, is malaria. The diagnosis can only be made with certainty by microscopic examination of the blood. The finding of the spirochæta or of the malarial parasite will at once settle the diagnosis, but a negative examination is of little value, although when dealing with a patient who has had no quinine, such a result would be in favour of tick fever. In dealing with natives, the occurrence of vomiting should suggest tick fever, as this symptom is rare in natives suffering from malaria. But in natives the diagnosis can only be made with certainty by the microscope.

In Europeans the vomiting is usually more severe and persistent in tick fever than in malaria, and the headache and pains are more marked. The reaction to quinine may cause error if the drug be given just before the crisis. The occurrence of a severe relapse in a patient who was being thoroughly treated with quinine would be in favour of tick fever. When a microscopical examination is not possible, the points in favour of the disease being tick fever are the severity of the headache, vomiting, and pains, the lack of reaction to quinine, and the irregular nature of the intervals between the febrile periods: in such a case inoculation of a monkey with a drop or two of blood from the patient's finger would aid the diagnosis. If the case were one of tick fever the monkey's temperature would rise in the course of a few days.

Where a microscope is available but the blood examination is negative, it would probably be worth while to puncture the liver with a hypodermic needle and make smears of blood drawn off this organ, for experiment with the disease in the monkey shews that the parasites are much more numerous in the liver than in the peripheral blood.

*Treatment.*—No drug so far tried is of any use either in cutting short the disease or in alleviating the symptoms. Since the discovery of the spirochæta of syphilis, mercury has been tried, but no results have yet been published. All that can be done is to keep the patient in bed, and give fluid diet when the vomiting allows of it being taken. When food cannot be taken by the mouth, recourse may be had to rectal feeding. In the intervals between relapses the patient should be kept quiet and given light nutritious diet. When the disease has run its course, the patient's condition will call for good food, tonics, and rest, until the lost ground has been made up.

**Prophylaxis.**—Prevention is easy for Europeans, and consists particularly in avoiding old camping-grounds and in tucking in the mosquito net so that a tick cannot enter. For natives, all that can be done is to avoid what are known to be infected camps, and to warn the natives against sleeping in old infected huts. Such huts should be burnt, and a camping-ground, when once it is known to be infected, should be abandoned.

**Immunity.**—A certain degree of immunity is conferred by an attack. In the monkey, reinoculation two months from the last relapse results in the appearance of scanty spirochætæ in the peripheral blood. But the interval between inoculation and the appearance of the parasites is prolonged (ten days), and their appearance is not accompanied by any rise in temperature. This explains why natives suffer from a much shorter and milder form of the disease than do Europeans. The native, living in an infected hut, is constantly liable to fresh infection. As the immunity conferred by one attack wears out he may be reinfected, but, as a result of the previous attack, he is not as susceptible as a newcomer. He possesses a certain amount of resistance to the disease, and one attack is sufficient to raise his degree of immunity to the point which is only reached in the European after many relapses.

**The Disease in Monkeys.**—The course of the disease in the monkey is shewn in Chart III. The animal is evidently ill during the febrile period, and refuses its food. In the intervals it appears well, and there is little loss of condition during the disease. Examination of the blood shews the spirochætæ to be present in great numbers during the fever, but they disappear suddenly at the crisis. Coinciding with the rise of temperature, there is a marked leucocytosis with relative increase of the polymorphonuclear leucocytes. These cells and the large mononuclears frequently shew vacuolation, and a parasite may sometimes be seen in the vacuole in a more or less advanced stage of degeneration.

When death occurs the temperature falls below normal, but the spirochætæ can still be found in great numbers. The animal becomes comatose and dies. The liver and spleen are usually found to be slightly enlarged, and petechiæ may be found on the surface of these organs and of the lungs and kidneys. The bone-marrow is dark in colour and congested. The parasites are found in great numbers in smears of lung and liver, but are scanty in the bone-marrow and spleen. Beautiful illustrations of phagocytosis can be seen in the liver and lung smears.

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P. H. R.



## THE SPOTTED FEVER OF THE ROCKY MOUNTAINS

By LOUIS W. SAMBON, M.D.

SYNONYMS.—*Spotted Fever, Black Fever, Black Measles, Blue Disease, Tick Fever, Piroplasmosis hominis.*

**Definition.**—An acute infectious disease of about two weeks' duration, occurring sporadically, during the spring months, in some of the valleys of the Rocky Mountain Plateau, and characterised by a petechial eruption, accompanied by fever, enlargement of the spleen, and marked nervous symptoms.

**History.**—For over thirty years the spotted fever of the Rocky Mountains has been looked upon as a distinct disease by the physicians of Montana and Idaho, and in 1899 Maxey refers to it as "an independent, specific disease, and related in no way to any disease described in our text-books on practice." The first published account of the malady appears to be a summary given by Lieut.-Col. W. M. Wood, U. S. Army, at Boise Barracks, Idaho, in 1896; and the earliest recorded cases were in 1873, in the Bitter Root Valley, in Montana. Some authors believe that the Indians were subject to spotted fever prior to the advent of white men, but Wilson and Chowning, who investigated the disease for the Montana State Board of Health in the spring of 1902, in the Bitter Root Valley, were unable to obtain any reliable information as to its occurrence among the Indians, who, until 1890, inhabited the valley. In July 1902, Wilson and Chowning announced that they had discovered an intracorpuseular parasite of the genus *Babesia* (= *Piroplasma*) in the red blood-cells of patients suffering from spotted fever. At the same time, they incriminated a tick *Dermacentor reticulatus* (= *identalis* Marx and Neum.), as the possible carrier of the infection, and suggested that the burrowing squirrel or common grey spermophile (*Sciurus hudsonicus*) might be the regular host of the parasite they found in man. Their observations were confirmed by F. F. Wesbrook and O. Cobb in 1902, and by J. F. Anderson in 1903. In May 1904, C. W. Miles visited the Bitter Root Valley to study the disease from a zoological standpoint. He examined microscopically fresh and stained preparations of blood from nine characteristic cases of spotted fever, and also a slide received from Wilson and Chowning, but failed to find any *Babesia*. Moreover, he found no evidence that the burrowing squirrel was the original host of the parasite of spotted fever, or that the tick was the carrier of the infection.

**Geographical Distribution and Etiological Factors.**—Spotted fever has been reported in several of the Western States of the American Union—Idaho, Montana, Wyoming, Utah, Nevada, Oregon, Washington, and also in the territory of Alaska (Gwinn and M'Cullough).

*Topographical Distribution.*—The disease is found in the valleys, most observers point out that it is contracted while the patients residing or sojourning in or near the foothills of the mountains. In the Bitter Root Valley the disease is confined to the west side of the river, and more precisely to the eastern foothills of the Bitter Mountains. The west side is narrower than the east, it is watered by more numerous mountain streams, and has much more timber and underbush.

*Seasonal Distribution.*—Almost without exception authors are of opinion that the incidence of spotted fever is confined to the spring months. It appears in March and continues until the latter part of June. According to M'Cullough it has occurred as early as January and as late as July.

*Epidemic Character.*—Spotted fever occurs sporadically, and, although Sweet says that several cases may appear in a household, it is excepted to find more than one or two in the same house. The majority of writers regard the disease as non-contagious. The disease attacks alike persons of any age or either sex; those who go for business or pleasure to the lower ranges of the mountains in the spring are specially liable to suffer.

*Morbid Anatomy.*—Examination after death shews nothing particularly characteristic. The skin presents the petechial rash. The blood is dark and fluid. The muscles are of a deep red colour. The myocardium shews an acute parenchymatous degeneration. The lungs are usually congested. The spleen is enlarged, of a slaty purple colour and soft. The liver is slightly enlarged. The kidneys are hyperæmic and swollen. There are no important changes in the brain and spinal cord; the blood vessels are somewhat congested.

*Symptoms.*—The duration of the *incubation-period* is uncertain. According to Anderson, it may vary from three to seven days. Boeck places it at from ten to twenty-one days. Stiles has shewn that the disease may develop within six days.

*Onset.*—In many cases, the disease sets in suddenly with a severe rigor; in others, it comes on gradually with lassitude, general malaise and chilliness. As a rule, the period of invasion is marked by severe headache and backache. The patient is restless and sleepless. The face becomes flushed, dusky and slightly œdematous, his eyes congested, his expression listless, dull, and heavy. The temperature rises rapidly and the skin becomes dry, hot, and pungent. The pulse is full and accelerated. The tongue becomes furred and inclined to tremble. Nausea is common, and vomiting may be an occasional symptom. Frequently, there is evidence of a slight bronchitis from the outset.

*Eruption.*—The most characteristic feature of the disease is the peculiar exanthem. It commences usually from the fourth to the seventh day of the disease—sometimes later, occasionally earlier. It appears first on the back or about the ankles and wrists, extending in two or three days over the entire body. On first appearance,

eruption consists of unelevated, rose-coloured spots varying in size from 1 to 5 mm. in diameter. Each spot is irregular in outline, fades insensibly into the hue of the surrounding skin, and disappears completely on pressure. In two or three days these spots undergo a marked change. They increase in size, assume a purplish colour, do not disappear on pressure, and become petechial. About the fourteenth day, the eruption begins to fade, but it may remain faintly visible for many weeks. Its disappearance is followed by a branny desquamation of the cuticle which is hardly noticeable. In addition to the eruption, the skin is always jaundiced to a greater or less degree, and the yellow discoloration is well marked in the conjunctivæ.

*Fever.* As a rule, the temperature rises abruptly, especially when the disease commences with a rigor, and it may reach 102°, 103°, or even 104° F. on the evening of the first day. Then it steadily ascends with slight morning remissions during the first four or five days. The fastigium is usually attained by the fifth day, when the temperature may be as high as 105°, 106°, or even 107° F. In mild cases it seldom rises above 103° F. Having reached its acme, the fever continues until the tenth, twelfth, or fifteenth day, when it begins to decline. Defervescence most commonly occurs by lysis.

*Pulse.*—Full and strong at first, the pulse later becomes soft and weak, but rarely dierotic. It gradually becomes more rapid, and, though it may not be above 100 throughout the whole course of the disease, it may reach 130 or 140 in severe cases. Slight catarrh of the *respiratory tract* is always present from a very early period of the disease, and the respirations are more or less increased in frequency.

*Ingestive Tract.*—The tongue is clammy and furred at the outset; later, it becomes shrivelled, dry, brown, and tremulous, and sordes accumulate on the teeth and lips. Anorexia and nausea are common, vomiting rare. As a rule there is constipation, but in some instances there is diarrhoea associated with abdominal distension and slight tenderness. The *spleen* is tender and enlarged early in the disease, and may extend one or two inches below the ribs. The *liver*, though it may be somewhat enlarged, is not tender. The *lymphatic glands* in the neck have in a few cases been found enlarged, and Anderson reports enlargement of the axillary glands in one case. *Epididymitis* is frequent, and sometimes severe. The *blood* becomes thick and dark, its coagulation-time is considerably prolonged. The erythrocytes are slightly reduced in number, and their hæmoglobin diminished. The large mononuclear leucocytes are increased.

*Urine.*—The urine is usually scanty, acid, deeply coloured, and of high specific gravity. It frequently contains a trace of albumin, numerous tubercasts, and much granular debris.

*Nervous System.*—Great prostration is constant. Headache is intense and persistent; it is generally frontal, but may be temporal or occipital. It is accompanied by giddiness and ringing in the ears. Backache, chiefly in the lumbar region, is often distressing. Pains in the legs are not uncommon, and the patient invariably complains of general soreness.

The mind is usually clear early in the disease, but by degrees the patient becomes stupefied, and there may be a quiet muttering delirium or violent raving. Coma and death usually follow the delirium. Occasionally there may be convulsions before death, which is usually from exhaustion. Convalescence is usually rapid (Figgins), but some authors state that it may be prolonged for months.

*Complications.* — Hypostatic pneumonia and gangrene of the toes, hands, scrotum, and nose are frequent complications.

*Mortality.* — There is a striking difference in the mortality of the disease between the States of Idaho and Montana. In Idaho it is about 2·5 per cent, in Montana from 70 to 80 per cent, and in some years even 90 per cent.

*Diagnosis.* — Spotted fever may be mistaken for measles, small-pox, purpura, cerebrospinal meningitis, relapsing fever, or enteric fever; but in comparing typical cases there can be no possible confusion because spotted fever presents very distinctive characters.

*Relation of Typhus Fever and Spotted Fever.* — It is impossible to distinguish spotted fever from typhus fever, and I am inclined to think that they are identical. Those who have had the opportunity of studying the disease believe, however, that the spotted fever of the Rocky Mountains differs from typhus both clinically and epidemiologically. Clinically, because it has a shorter period of incubation, because its rash appears first on the extremities, its nervous symptoms are less pronounced, and its termination is by lysis. Epidemiologically, because it is limited to the spring months, and is non-contagious. These distinctions are illusory. As to the period of incubation no comparison is possible because it has not been determined definitely in either disease. Several authors state that the rash of spotted fever usually appears first about the ankles and wrists, others state that it commences on the face or back. In typhus fever the eruption frequently begins on the extremities. The nervous symptoms do not differ, but their intensity may vary exceedingly in both diseases. As to termination, it is incorrect that typhus fever always terminates by a sudden crisis; the most common form of termination being by lysis. The seasonal difference put forward by some authors is no better grounded. Typhus fever is pre-eminently a disease of the spring months, although it may also prevail at other seasons under special conditions. On the other hand cases of spotted fever in January, February, June, July, and August have been reported. As to the question of contagion, attention may be drawn to published instances of husband and wife or two children contracting spotted fever at about the same time. Stiles considers that, despite the general experience regarding the non-contagiousness of the disease, such close intimacy as sleeping in the same bed may perhaps lead to infection of a healthy individual. But are we right in considering typhus fever as contagious? It is true that all our text-books describe it as such, and that Professor Osler says it is "one of the most highly contagious of

febrile affections." But yellow fever, relapsing fever, and other diseases, until quite recently generally regarded as contagious, are now known to be conveyed by the means of intermediary agents. A careful study of the epidemiology of typhus fever leads, I think, inevitably to the conclusion that the disease is not immediately contagious. In its endemic centres typhus fever usually appears sporadically year after year without giving rise to epidemics. In certain years, however, especially after the depressing influence of war and famine, there may be an enormous increase in the number of cases, and the disease takes on epidemic proportions just like malaria, yellow fever, and relapsing fever, under very favourable etiological conditions. In its epidemic outbursts, typhus fever attacks almost exclusively the lowest classes, and more especially the inmates of crowded dwellings, such as jails, asylums, and lodging-houses. It has prevailed frequently on ships, or in army camps, with all the appearances of an exceedingly contagious disease. The experience of hospitals is most instructive. In badly constructed, uncleanly hospitals the disease has frequently spread to other patients, and attacked doctors, nurses, and attendants; in others, better cared-for patients and staff have remained unaffected, notwithstanding the admission of numerous cases. As in relapsing fever, the virus of typhus fever is able to persist for a long time in rooms that have been occupied by the sick, and old clothes and bedding have often been the means of conveying it to a distance. Outbreaks of typhus fever have often followed on the arrival of famine-stricken hordes though not suffering from the disease. Remarkable examples were witnessed in 1868, in Algeria, when many of the persons attending to the relief of the famished natives were attacked, notwithstanding that their contact had been of the slightest and invariably in the open. These and other facts in the epidemiology of typhus fever are, to my mind, only capable of one interpretation, namely, that the disease is not immediately contagious, but that it is transmitted by blood-sucking parasites such as the common bed-bug, or the body-louse, and, possibly, the flea. Further arguments in favour of this view are the well-known frequent association of typhus fever with relapsing fever (*vide* vol. i. p. 1186), and the notable decrease of both diseases in consequence of the expulsion of the bed-bug and other vermin by habits of greater cleanliness in households.

**Etiology.**—In Idaho spotted fever has been ascribed to drinking the water from creeks and surface wells, and some of the local physicians attributed it to malaria. Wilson and Chowning were the first to describe a specific organism as the cause of the disease. They specially point out that bacteriological cultures did not shew the presence of any causal bacteria, and they describe bodies which they interpret as protozoa, and called "*Pyroplasma hominis*" (namely, *Babesia hominis*). They further state that they inoculated rabbits with blood of spotted fever patients, and recovered the parasites from the blood of the inoculated animals. Wilson and Chowning's observations were confirmed by Cobb, Westbrook, and Anderson, but contradicted by Stiles who failed to find any *Babesia*

or other organism in either patients suffering from spotted fever, or in rabbits inoculated with blood from fatal cases. Without material at hand it is of course impossible to give any opinion as to Wilson and Chowning's results; it is, however, interesting that at about the same time, Gotschlich in Egypt announced the discovery of a *Babesia* in cases of typhus fever—and that other investigators such as Thoinot and Calmette had previously described protozoa in connexion with the latter disease. Whatever may be the value of Wilson and Chowning's observations, there is much in favour of the protozoan nature of spotted fever. The disease is undoubtedly a hæmic infection, and the mononuclear increase is certainly in favour of a protozoan parasite. Wilson and Chowning suggest that spotted fever is probably transmitted by ticks. They were led to this hypothesis not only because they believed the disease to be caused by a babesia, but because in most of the cases there was evidence or, at least, a history of tick bites. Stiles opposes this on the ground that there is no proportion between the limited number of cases and the great frequency of tick bites in the Bitter Root Valley where *Dermacentor reticulatus occidentalis* is exceedingly common. The suggested identity of spotted fever and of typhus fever might at first sight appear to be a further argument against the hypothesis that spotted fever is transmitted by ticks; but on the analogy of relapsing fever, which is conveyed by ticks in Africa and Asia, and by the common bed-bug in Europe, this method of transmission appears reasonable. Whatever may be the real nature of spotted fever, its causative agent must be closely allied to that of typhus fever, and I have no doubt that the elucidation of the disease of the Rocky Mountains will advance our knowledge of the etiology of typhus fever.

**Treatment.**—The disease is self-limited, and a large proportion of cases recover without any treatment. Drugs indeed have no effect upon the disease. Wilson and Chowning suggest the use of quinine in large doses, preferably hypodermically, but it has often been used without result. Normal saline solution in rectal, vesical, and subcutaneous injections are said to have been beneficial. Most authors recommend the drinking of large quantities of water. The treatment is entirely symptomatic: Salines, calomel, or enemas for constipation; cold sponging for high temperature; Dover's powder to relieve pain and restlessness, and cardiac stimulants when necessary. The patient should be frequently turned in bed after the disease is well established, in order to prevent hypostatic pneumonia. The diet should consist of milk, broths, and eggs.

**Prophylaxis.**—Definite statements regarding prevention cannot be made until the cause of the disease and its method of transmission are definitely known. Meanwhile, the destruction of ticks and the avoidance of their bites seem reasonable.

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L. W. S.

## YELLOW FEVER

By ANDREW DAVIDSON, M.D.

SYNONYMS.—English, *Black vomit*; French, *Fèvre jaune*; Spanish, *Fiebre amarilla*, *Vomito negro or prieto*; Italian, *Febbre gialla*; German, *Gelbfieber*; Latin, *Typhus icterodes*.

**Definition.**—Yellow fever is an infectious disease, characterised by a continued fever of two or three days' duration, followed by a remission ending in convalescence or passing into a critical stage, marked by jaundice, black vomit, passive hæmorrhages, albuminuria, suppression of urine, and nervous and mental disturbances.

**Endemic Habitats.**—Yellow fever is endemic in three regions—the West Indies and the adjacent coast of Mexico, the Senegambia and Ivory coasts of Africa, and Brazil. Three points in particular stand out in the story of yellow fever. (i.) Its comparatively recent appearance in each of these regions; (ii.) the long intervals during which it has been absent from every individual locality in these endemic areas; (iii.) the frequency with which its reappearance can be traced to importation by shipping from infected centres.

**West Indies.**—The first outbreak that can be recognised with certainty as yellow fever is that which appeared at Barbadoes in 1647. That this is the true typhus icterodes is to be inferred not so much from its having been "as killing as the plague" as from the significant circumstance that it extended its ravages to the shipping in the harbour, by which it was introduced into St. Christopher and thence to Guadeloupe. The symptoms, moreover, were quite characteristic, which cannot be said of earlier epidemics supposed to have been yellow fever. Yellow fever broke out in Cuba for the first time, so far as can be ascertained, in 1548-49, i.e. about 140 years after the Spaniards settled in the island. The first accounts of its appearance in Jamaica date from 1655: in San Domingo from 1656; in Martinique from 1688; at Vera Cruz from



1690 ; and in St. Thomas as late as 1793. During the seventeenth and eighteenth centuries yellow fever was apparently absent from each of these islands for long periods of years. Barbadoes, for example, enjoyed immunity from 1647 to 1690, when the disease again broke out, and was known as "The new pestilence" or "Kendal's disease." The inhabitants of Barbadoes would hardly have bestowed upon it such designations if it had been then of frequent occurrence in the island and well known in the West Indies. Another break of fifty-four years occurred in this island between 1739 and 1793. In San Domingo nothing very certain is heard of it for the thirty-five years, 1746-81, and about the same period it was absent for thirty-eight years from Jamaica. It appears to have been unknown in Cuba from 1656 to 1678, from the latter date on to 1702, and again from 1706 to 1746. Similar gaps occur in the epidemiological records of yellow fever in the other islands. Although unrecorded outbreaks no doubt occurred, the broad truth remains that yellow fever has been absent for long series of years from every spot in its West Indian habitat.

No less remarkable is the ever-recurring mention of the transit of yellow fever backwards and forwards from island to island by ships. So far back as 1698 the importance of this mode of transport had become so well recognised that in that year a quarantine ordinance was passed in San Domingo, applying to ships coming from the Windward Islands "in order to prevent the introduction of the Mal de Siam," as yellow fever was then called. It is also clear from this that the inhabitants did not look upon it as permanently endemic in their midst. The frequency, too, of outbreaks at different places seems to have borne a direct relation to the activity of trade between towns within the yellow fever zone and to the numbers of susceptible strangers resident in a locality.

*West Coast of Africa.*—Whether yellow fever be indigenous to the coast, and was carried thence in connexion with the slave trade to the West Indies, or whether it was introduced into Africa from the latter cannot now be determined with any certainty. The first unimpeachable evidence of its existence in this region dates no further back than the year 1778, when it was epidemic at St. Louis in Senegal. From Schott's account of this outbreak, as well as from subsequent observations, we find yellow fever on the West Coast of Africa, as in the West Indies, being carried from place to place by maritime commerce, and having periods of outbreak followed by considerable intervals of absence.

*Brazil.*—As a constant element in the nosology of Brazil, yellow fever dates from the last quarter of 1849, when it was introduced from Havana or New Orleans, or from both. From that time onwards, deaths from this disease have been registered every year in Rio, with the exception of 1865. The annual mortality fluctuates greatly, remaining high for three or four years in succession, then sinking to a minimum.

It is from these three centres that yellow fever has been propagated to other parts of America, to Europe, to the Congo Coast, and to the West African Islands. The continents of Asia and Australia, the Pol-

Asian Islands, the eastern coast of Africa, and the greater part of Europe have hitherto escaped this pestilence.

**Area of Diffusion.**—From the West India centre yellow fever has been carried, times without number, to the Gulf and Atlantic coasts of America, and to towns on the Mississippi, those most frequently infected being the southern sea and river ports in constant communication with the West Indies. The Pacific coasts of Central America, cut off from direct sea communication with the West Indies, have suffered little. The North Atlantic coast of South America, from the Gulf of Darien to Cayenne, has been subject to frequent outbreaks. After yellow fever became domesticated in Brazil, it has been introduced more than once into Monte Video and Buenos Ayres; it has penetrated up the Parana to Corrientes and Asuncion. It was carried to Peru for the first time in 1854, where it threatened to become endemic. Guayaquil was visited in 1740, in 1842 and, according to Nelson, the outbreaks of late years are so frequent there that this port may now be looked upon as an endemic seat of the disease.

With the exception of an outbreak at Leghorn in 1804, all the fatal epidemics of yellow fever in Europe have been restricted to the Iberian peninsula, and the Balearic Islands, and up to the time when it obtained a footing in Brazil, the disease had always been imported from the West Indies. Yellow fever made its first appearance on European soil at Cadiz, the headquarters of the West Indian trade, in 1700, and subsequently in 1730-34, 1741, 1764, and 1780. Lisbon was attacked in 1724, and Malaga in 1741. Respecting the eighteenth century epidemics it has to be observed that, while some were destructive, none of them shewed any tendency to spread inland or even to any extent along the coast. It was very different in the great outbreaks of 1800-4, 1810-1813 and 1819-20. These were of an intense type, attacked in some instances almost the entire population of the invaded localities, caused a great mortality, and exhibited a tenacity and power of diffusion not observed in the earlier epidemics. They spread not only along the coast, but extended for a considerable distance into the interior, making great havoc in Seville, Murcia, Jumilla, and other inland cities. The later outbreaks in 1823, 1828, 1870 were milder and more distinctly localised. The last of the series was an outbreak at Madrid in 1878. On all former occasions when inland towns were invaded, it was by extension from a previously infected coast town. On this occasion it was carried direct from Cuba to Madrid, declaring itself immediately after the return of troops from Cuba, among whom no case of fever had occurred during the voyage, in a street where the discharged soldiers had taken up their quarters. It appeared on the 15th of September, and after attacking about fifty persons and causing some thirty five deaths, it died out in the middle of October. Lisbon, which remained free from yellow fever during the first half of the nineteenth century, experienced two outbreaks—one in 1850, and the other in 1856-57, after the disease had established itself in Rio, a port with which Lisbon is in constant communication.

A few outbreaks of a limited kind have occurred in France—that of St. Nazaire in 1861, which, having been very carefully observed and recorded, is of considerable etiological interest (*vide* p. 330).

The only instance in which yellow fever can be said to have effected a lodgment on our shores was in 1865, when the infection was introduced into Swansea from Cuba. Its attacks were restricted to those who had been in direct communication with the infected vessel or who lived within two hundred yards of the spot where she was berthed; in all the cases numbered thirty, and the deaths seventeen (4).

The extensions of yellow fever from the Senegambia coast have been few, and limited mainly to the West African Islands. A very remarkable epidemic of what appears to have been true yellow fever occurred in 1891-92 at various military posts in Upper Senegal, 750 miles from the coast, at a time when it was absent from the coast region, and had not been seen in Upper Senegal for ten years. The natives at the same time appear to have been suffering from some epidemic disease, the nature of which was not sufficiently investigated. This incident recalls to our mind Pym's doctrine that yellow fever is a disease of the interior of Africa, where he believed it to exist in a modified form among the native races.

**Endemic and Epidemic Characters.**—The conditions necessary for the endemicity of yellow fever are (a) a winter temperature of about 68° F.; (b) the presence of the insect host; (c) a supply of susceptible subjects.

Epidemics of yellow fever are of three kinds—(a) autochthonous occurring in endemic areas; (b) exotic, from the introduction of the disease into localities outside its endemic habitats; (c) non-propagable outbreaks beyond the range of its insect host.

Autochthonous epidemics continue throughout the whole year, and persist until the supply of susceptible subjects is exhausted. Exotic epidemics, on the other hand, are arrested by the approach of winter, and fresh outbreaks depend, as a rule, on a new importation of the virus. The introduction of a yellow fever patient in the early stage of the disease into a town in the exotic zone where the *stegomyia* exists is sufficient to start an epidemic. As non-propagable outbreaks occur outside the range of the *Stegomyia fasciata*, the introduction of a yellow fever patient into such a locality cannot give rise to a spreading infection. Non-propagable outbreaks are caused by infected mosquitoes, and only those exposed to their bites suffer. These distinctions, although hitherto overlooked, are real and important.

When yellow fever is introduced by a person suffering from the disease into a locality where the *stegomyia* is present, from twelve to fourteen days elapse before new cases occur, and these appear in the house of the patient or its immediate neighbourhood. An instance is, however, recorded by Bryson in which the interval appears to have been only ten days. When, on the other hand, the disease is introduced by infected mosquitoes it manifests itself within a few days, and exc

even among those exposed to their bites, and secondary cases appear after a fortnight, and it may be, in different parts of the town. The disease then spreads with a rapidity proportional to the density of the susceptible population, the number of *stegomyia*, the freedom of intercourse between the healthy and the sick, the degree of temperature at the time, the extent of overcrowding, and the want of free ventilation. Insanitary conditions, so common in the districts of seaports adjoining harbours and wharves, such as collections of surface-water, stagnant gutters, and foul drains, favour its spread and increase its malignancy. The duration of an epidemic is partly determined by these local conditions, partly by the weather, and the number of susceptible subjects, but largely also, by the season of the year at which the infection is introduced, and to some extent by the type of the particular outbreak.

**Virus and Modes of Transmission.**—Finlay of Havana, so far back as 1881, formulated the hypothesis that the virus of yellow fever is inoculated by the *Culex* mosquito. His views, which underwent various modifications, failed to attract attention, until the demonstration by Professor Ronald Ross of the agency of the anopheles in the transmission of malaria removed the *a priori* improbabilities that had before militated against the serious examination of the hypothesis. All researches were up to then directed to the discovery of a bacterial virus. It would be tedious to enumerate the various micro-organisms that were from time to time announced as the virus of yellow fever. Sanarelli's *Bacillus uterinus* had better claims for consideration than most of them, as it is undoubtedly present in a certain proportion of the cases, and is, moreover, capable of giving rise in man and several of the lower animals to some of the more characteristic symptoms and lesions of yellow fever. I refer to it now, it is because this bacillus when present may, after all, be found to play a subordinate but not insignificant part as a micro-organism of secondary infection in aggravating the character of the disease.

An American commission, appointed in 1900, consisting of Reed, Carroll, Agramonte, and Lazear, took up the investigation of yellow fever on new lines, and proved the inoculability of the disease by the blood of yellow fever patients, its transmissibility by the *Stegomyia fasciata*, and confirmed experimentally—what experience had already taught the non-communicability of the infection, in ordinary circumstances, by bedding and clothing soiled with the dejecta of yellow fever patients. The results arrived at by this commission have been abundantly confirmed by Guteras, Ribas and Lutz, Parker, Bever, and Pothier, and by the French Commission in Brazil (12). It will be sufficient here to state in the fewest words the facts which have been established by these researches, and then to notice certain points which still remain unsettled.

A. 1 The virus of yellow fever is present in the blood during the first three days of the fever. It is generally absent from the fourth day of the disease, even when the fever remains high. Whether it is present in the blood during relapses is still uncertain.

2. The inoculation of the blood of a yellow fever patient, during the first three days of the sickness, whether fresh, defibrinated, or filtered through a Berkefeld laboratory filter, gives rise to the disease in the susceptible. The microbe also passes through the Chamberland porcelain filter F., but seems to be arrested by the filter B.

3. The serum heated for ten minutes at  $55^{\circ}$  C. (according to the French Commission for five minutes) loses its virulence; and the same result is found to follow keeping the serum in a test-tube, plugged with cotton-wool, for forty-eight hours in the dark, and at a temperature of  $24^{\circ}$  to  $30^{\circ}$  C.; but the serum retains its virulence for five days when preserved under oil or vaseline.

4. Small quantities—2 c.c. to 0.1 c.c.—of yellow fever blood, injected hypodermically, suffice to give rise to an attack.

5. A drop of virulent serum applied to, and left to dry on, a square centimetre of excoriated skin failed to produce the disease.

6. Some experiments indicate that virulent serum heated to  $55^{\circ}$  C. for five minutes, and the serum of convalescents, possess the property of preventing the infection or of rendering it milder. The latter appears further to have a therapeutic action. These results, however, require confirmation.

7. The laboratory animals hitherto experimented on, including five species of apes, have proved refractory to blood inoculations.

The fact that yellow fever, like malaria, is communicable by inoculation, suggests that it also is normally transmitted by the agency of some suctorial insect.

B. 1. The cardinal fact, viz., that the *Stegomyia fasciata* fed on yellow fever blood is an agent of infection has been placed beyond doubt by repeated and carefully conducted experiments. The only point open to discussion is whether yellow fever is solely propagated in this way. That it is normally transmitted by the stegomyia is certain. The bite of one mosquito has proved sufficient to cause yellow fever.

2. The disease conveyed by the mosquito is true yellow fever, exhibiting the characteristic symptoms of the malady, and running a normal course in a mild, severe, or fatal form.

3. The mosquito fed on yellow fever blood is not capable of giving rise to the infection until after the lapse of twelve or fourteen days. Experiments with insects fed from two to ten days have, hitherto, proved negative. The infected mosquito has communicated yellow fever fifty-seven days after contamination, and there is reason to believe that it is more virulent after it has been contaminated for a considerable time, especially if kept at a temperature of  $27^{\circ}$  or  $28^{\circ}$  C.

4. The bite of the infected mosquito does not necessarily cause yellow fever. About 35 to 40 per cent of experiments of this kind prove negative.

5. Marchoux and Simond appear to have established the transmission of the virus of yellow fever to a new generation of insects. In February 1905 the eggs of a stegomyia, aged twenty days, which had been fed on



Several yellow fever patients were hatched, and after their metamorphosis the insects were fed on glucose for fourteen days. On the 2nd March two of these *stegomyias* were made to bite a susceptible person newly arrived in Brazil from Portugal, and who was not exposed to the infection. No reaction followed. The same person was bitten again by one of these two mosquitoes on the 10th of March. Four days later, viz. on the 14th the subject of the experiment was seized with fever and went through a mild but typical attack,—the vomiting, pains, march of temperature, and icterus were quite characteristic. After the patient recovered he was repeatedly bitten by infected mosquitoes, but proved immune. It will be observed that the subject of this experiment was twice bitten, and it was only after the insect was fed on blood that infection took place. Another point to be noticed is that the experimental disease was of a mild type, possibly owing to an attenuation of the virus in its passage. Previous experiments of this kind proved negative, and the precise conditions under which the virus is so transmitted are still unknown.

C The virus of yellow fever has not been discovered either in the blood of the patient or in the body of the mosquito. It apparently belongs to the ultra-microscopic class of parasites. That it is a parasite may be safely inferred from the analogy of other infective diseases. From the fact of its alternate passage through a vertebrate and insect host, and that, like the parasite of malaria, it requires a certain time for its development in the mosquito, it is probable that it belongs to the protozoa. There is no reason to suppose that it is a parasite of the blood corpuscles. The view that the virus is of the nature of a toxalbumose, as suggested by Treille, is altogether inadmissible.

D It has not been proved that the bite of an infected mosquito is the only way in which the disease is conveyed to man, nor that the mosquito can derive the infection from any source other than a yellow fever patient; but no other mode of conveying or acquiring the infection is known. The question of the transmissibility of the virus beyond the second generation of mosquitoes is undecided, and there is no evidence for or against the existence of an extra-corporeal phase in the life of the parasite.

**Etiology.**—We shall first notice some of the etiological peculiarities which distinguish yellow fever from other epidemic diseases, and then consider, more briefly, other factors which enter into its causation.

1 Yellow fever is notably a disease of *seaports* and *river-ports*. It is in seaports that it is endemic; from these it spreads, and in these the great epidemics occur. The instances of yellow fever outbreaks in inland localities are comparatively rare: some of these have already been noticed, as, for example, its spread to inland towns of Spain in 1800-4, the outbreak in the hinterland of Senegal in 1891-92, and its appearance in Madrid in 1878. In the severe epidemics of 1873 and 1878 in the United States, yellow fever shewed a tendency to invade localities at some distance from sea and river. In recent years, since railway

communications have been opened up between yellow fever ports and interior, instances of this kind have become more numerous. St informs us that the disease has spread inland, in Brazil, along the line of railway to places hundreds of miles from the coast, and that the town of S. Carlos, a long way in the interior, has been decimated on more than one occasion. But it is doubtful whether yellow fever will succeed in establishing itself in the interior of continents, and whether the land can replace the ship as a vehicle of its diffusion.

The predilection of yellow fever for seaports is due to three factors: (a) the prevalence in these of the *Stegomyia fasciata*; (b) the constant arrival of sailors and passengers from countries outside the yellow fever zone, who are therefore specially susceptible; and (c) the opportunities they afford for the introduction of the malady by the circumstances of their intercourse with infected places. To realise the great importance of the second of these factors, it is sufficient to recall that the widespread series of outbreaks, extending from 1793 to 1804, of which the epidemics in Spain in the nineteenth century were episodes, were sustained and kept going by the presence in the West Indian waters of the fleets and troops of different nationalities, the occupation of islands where the disease was latent or active by large bodies of unacclimatised soldiers and sailors, and the migrations of the civil population from one place to another on account of military and revolutionary movements.

2. Since yellow fever is a disease of seaports, it follows that it is mainly restricted to *low altitudes*. No definite altitudinal limits can be assigned to its spread. These will depend on the existence or non-existence in a locality of conditions compatible with the temporary or permanent presence in it of the *stegomyia* and its proximity to an infected port. Temperature is here the chief, but not the sole determining element. Petropolis, near Rio de Janeiro, at an elevation of 1500 feet, with a mean winter minimum temperature of 20° C., has remained completely exempt, notwithstanding that a large portion of the population spends the day in the city, returning home at night. Cases are frequently imported, but the disease does not spread, the *stegomyia* being absent. St. Paulo, on the other hand, to the south of Rio, at an elevation of 2000 feet, with a mean minimum of 16·1°, has lately suffered from somewhat severe outbreaks. Newcastle, in Jamaica, at an elevation of 4000 feet, has had two visitations—one in 1856, and another in 1891. Humboldt fixed the limits of the vomito on the slopes of the Mexican Sierras at 3243 feet, but in 1902 it appeared in villages near Orizaba and Jalapa at elevations of 4108 to 4330 feet—the highest point at which non-imported cases have been observed—and it is stated that the appearance of the fever in these places was heralded by the advent of the *stegomyia*. It is not, however, to be too hastily concluded that yellow fever can maintain itself and become in any sense endemic at high altitudes.

3. Another peculiarity of yellow fever is its limitation to *towns*, generally to towns of some considerable size. In this respect it differs



from malaria, which is more a rural than an urban disease. La Roche, in speaking of Charleston, says:—"The inhabitants of the surrounding country are sorely afflicted in certain seasons with remittent and intermittent fevers. To escape these they take shelter in the city, where such complaints do not prevail, but here they encounter the yellow fever, which, in its turn, never extends beyond the limits of the city." Yellow fever, it is true, is occasionally imported into villages situated near infected ports, and spreads in them, but it has never been known to become diffused to any extent in purely rural districts. This remarkable difference between the habitats of yellow fever and malaria, no doubt, depends upon the distribution and habits of their respective hosts. But yellow fever is not only confined to towns, but is often limited to a certain quarter of a city. The more elevated, airy, and hygienic districts frequently escape altogether, or are less severely visited, while the shore districts are being decimated. Bryson, referring to Freetown, in Sierra Leone, remarks that "the upper part of the town and the barracks where many Europeans lived, between whom and the infected part there was constant communication, entirely escaped. The line of demarcation was as complete as if it had been marked by an impassable barrier."

4. Yellow fever is a *house* infection. It is not in the street or the market-place that the disease is usually contracted, but in an infected house. Intercourse with the sick is free from danger. It is the sick-room, where the *stegomyia*, which is the common source of infection, lurks. The frequently repeated assertion that yellow fever is not propagated in hospitals is contrary to fact. A hospital is a house, and, like any other house, is liable to become infected. An infected house, *i.e.* one harbouring infected mosquitoes (not necessarily a yellow fever patient), is a danger to its inmates, hence the frequency of multiple cases in a family. Sometimes a house becomes a veritable lethal chamber for all who live in or enter it. An instance is recorded in connexion with one of the outbreaks in Spain, in which seventeen persons belonging to the family of Mr. Torret, surgeon, occupying one building, contracted the disease, fourteen of whom died. Every one, we are told, who put his foot within this fatal dwelling—doctors, nurses, priests, undertakers—all were attacked, until at last it was with difficulty that any one could be found to enter it in order to perform the last duties to the dead. Carter, referring to the outbreak at Orwood in 1898, states that "of forty-six persons non-immune who entered the house called 'Gray Mansion,' on or after the 21st of August, forty-five developed yellow fever, very few having any other exposure." The length of time that yellow fever may persist in a house is limited only by the life of the infected mosquitoes, which, according to Guitéras, may extend to 100 or even 154 days, although under normal conditions few live beyond 70 days. In certain circumstances, still imperfectly understood, the virus, as we have seen, may be transmitted to a new generation of insects, and this accounts for instances in which an epidemic has reappeared months after it had died out, without it being possible to refer it to a new importation of the disease.

5. Yellow fever differs from most other epidemic diseases in respect to the frequency with which it breaks out in ships, the extent to which its diffusion is effected by maritime commerce, and the tenacity and persistence with which it clings to an infected vessel. For this a yellow fever vessel, like a yellow fever house, is one which harbours infected mosquitoes. The old wooden ships engaged in the sugar, coal, and timber trades were more liable to develop yellow fever than modern steamships, which are better kept, lie for a shorter time at infected ports, and are not detained so long in the tropics on their homeward voyage. A ship becomes infected by lying in a port where yellow fever prevails, or from proximity to an infected vessel in port or at sea. Patients suffering from yellow fever may contaminate mosquitoes present on board, or insects already infected may be taken on board along with cargo or baggage. Mosquitoes may fly on board if the vessel is close to land, be wafted on board by the wind for the distance of half a mile at least, or transported by lighters to a vessel moored at a distance from the shore. The *Anne Marie* at St. Nazaire infected seven vessels lying near and to the leeward of her (*vide* p. 330).

In whatsoever manner introduced, mosquitoes shew a preference for certain quarters on board, which afford them shelter, warmth, water, or food. This explains the frequency with which yellow fever is confined to a particular part of a ship. They often take up their abode in the engine room or galley for warmth. In sugar ships the hold is naturally their favourite food resort. The presence of water attracts them. Dunlop mentions that on a submarine-cable vessel, the cable hands, who slept between decks on a level with and close to the openings of two large tanks in which the water covering the cable was contained, were practically the only sufferers. Occasionally they hide themselves behind boardings, or in some obscure place from which they only issue by night or when disturbed. When the infected insects are confined to the hold, no case, or only a few cases, may occur during the voyage, yet, when the hatches are opened for the discharge of the cargo, those engaged in this work, or otherwise employed on or near the vessel, are attacked. Instances of this kind are very numerous. When infected insects are secreted behind boardings the result is somewhat different. In the case of the *Donastierra*, which infected the town of Port du Passage in 1823, there was no disease on board on arrival, or for weeks before. The cargo was discharged without accident, and it was only when, a fortnight later, carpenters began to remove some decayed planks on the side of the vessel that the infection was let loose, as from a Pandora's box, upon those employed on or living near where she was lying. Exactly the same thing occurred on board *La Reine Victoria* in the port of Guayaquil in 1842. If the *stegomyia* has access to water, its life on board may be prolonged for a period of two or three months, and, as the mosquito is capable of breeding on board, a new

\* In this article a marvellous anticipation of the mode in which yellow fever is propagated will be found.

generation will have an opportunity of becoming infected when a succession of cases of yellow fever happen to occur at intervals during the voyage, and in this way the infection is maintained beyond the life-span of a single generation. It is extremely difficult to explain the swarms of infected insects that must have been present in some vessels in order to account for the numbers attacked, unless on the supposition that they had been bred on board.

A healthy port is contaminated by the introduction of a yellow fever patient or infected mosquitoes in all the ways in which a vessel is infected; but neither the patient nor the mosquito can give rise to an epidemic, properly so called, unless the *stegomyia* is a native of the locality. Outside the limits to which the *stegomyia* extends, the importation of the infection can only give rise to what we have called non-propagable outbreaks.

Many remarkable illustrations could be given of the tenacity with which the infection clings to a vessel. Thus, the crew of the barque *Hudson* at Sierra Leone were nearly all carried off with yellow fever in the early part of 1837, leaving the vessel in the harbour destitute of hands for the space of three months, during which time the fever had ceased in the Colony. When at the end of September fresh hands were induced by high wages to take her home, no sooner did they go on board the derelict vessel than they were seized with yellow fever, and set agoing a fresh outbreak in the Colony. The Portuguese emigrant ship *Maria da Gloria*, contaminated at Rio de Janeiro in 1874, had cases during her voyage to Lisbon, where she was put in quarantine and remained many weeks. On her return voyage to Rio a very severe outbreak of yellow fever occurred on board. Two other better-known instances that have been the subject of much discussion will be presently noticed.

6. Yellow fever is *par excellence* a disease of warm climates, and of the warmest months in the countries where it is endemic. We know of no other infection, the geographical range and seasonal prevalence of which are so clearly determined by temperature. Yellow fever can only maintain itself perennially where the mean temperature of the coldest months reaches  $20^{\circ}\text{C}$ . Within the endemic zone it is in the warm months that it assumes epidemic proportions, although its maximum prevalence does not coincide with, but follows, the maximum temperature. In the exotic zone, including the Mid Atlantic States of the Union, Spain, and Portugal, yellow fever does not assume an epidemic form until the day temperature has stood at  $26^{\circ}$  or  $27^{\circ}\text{C}$ . for some considerable time; but once the disease has declared itself, it will continue to prevail at a much lower temperature than that necessary for its development. A rapid fall of the thermometer is followed by an abatement of the epidemic, which becomes extinct when the temperature has fallen to freezing point, although sporadic cases may still continue to occur for some time. The recurrence of fresh cases in the succeeding spring or summer, without any evidence of fresh importation, as was sometimes observed in Spain,

shews that infected insects or their progeny can survive the winter of temperate climates. The relation of yellow fever to a high temperature depends on the fact that the evolution of the stegomyia is accomplished more rapidly when the temperature is high. Their multiplication is thus facilitated, and it seems probable also, from sundry observations, that they bite more readily, and that their bite is more virulent when the temperature exceeds  $26^{\circ}$  C.

Moderate rains alternating with periods of drought and sultry humid weather promote the epidemic prevalence of yellow fever. Heavy rains, on the other hand, check its progress, but the effect of rainfall depends largely upon the soil and drainage of a locality.

7. *Soil*.—Severe outbreaks of yellow fever have so frequently coincided with extensive disturbance of the soil as to suggest a causal relation between the two. This coincidence, to mention only a few cases, was observed at Natchez in 1823, 1837-39, and 1853, and at Charleston in 1842, 1852-54. Dr. Barton asserts that there has been no great epidemic of yellow fever in New Orleans except when there have been extensive excavations of streets or canals. Kermorgant traces the epidemic outbreaks in Upper Senegal in 1891-92, and again in 1897, to the same cause. In the same way he shews that the outbreaks of yellow fever at Grand Bassam, and that at Dakar in 1892, coincided with extensive upturning of the soil in these towns. Dr. Izett Anderson remarks that the soil has been extensively turned up on three occasions during the past twenty-five years at Kingston, Jamaica, viz., in 1872-73, 1876, and 1879, and on each of these occasions there has been a severe outbreak of yellow fever. The connexion between these outbreaks and soil disturbance may be due to the creation of numerous larger or smaller depressions, which become filled with water and form breeding-places for the stegomyia. Further observation must decide whether this is a full explanation of the phenomenon.

8. *Race, Residence, Acclimatisation*.—The white races are most susceptible to yellow fever, and in them it also assumes its most severe forms. The natives of the south of France, Italy, and Spain offer greater resistance to the infection than those of the north of Europe. Arab soldiers from Algeria have been found in Senegal and Mexico to be about equally susceptible as natives of the south of Europe. The American Indian is apparently little less liable than the European to yellow fever. The Chinese, on the other hand, are more resistant than white men. Nelson, who had a large practice among the Chinese merchants at Panama when the work on the canal was going on and yellow fever was prevalent, did not see or hear of a case among them, and others have recorded a similar experience. The circumstances of a community have, however, to be taken into account. It is doubtful if the Chinese at Panama would have escaped, as they did, if they had been employed as labourers on the canal. At any rate, in other places and circumstances, the Chinese have succumbed to the disease in considerable numbers. The negro race exhibits the most marked resistance to the

on. In mild epidemics negroes often escape entirely; in severer attacks, they are less liable to contract the disease than the whites, when they happen to do so, have it in a milder form. In the severe epidemic at Decatur in 1878, the case-mortality among the white population was 44 per cent, that of the negroes 13 per cent. Here both were living under the same climatic conditions and equally exposed to infection. Negroes who have been born and brought up in the tropics are somewhat more susceptible than those living in the temperate zone. There are probably different degrees of resistance among the different tribes of negroes, just as there are different degrees of susceptibility among the whites. A body of 500 Nubians and Sudanese, which accompanied the French expedition to Mexico in 1862, remained entirely immune while the French and Mexican troops were being decimated by yellow fever. As yellow fever is unknown in Nubia and Senegal, this extraordinary insusceptibility cannot have been owing to their having passed through the disease in infancy, nor is it to be attributed to the fastidiousness of the *stegomyia* in refusing to feed on the negro. The French Commission to Brazil found that although the mosquito does shew a preference for the white man, especially for the young and vigorous, with a delicate skin and fair complexion, it will, nevertheless, readily enough attack the negro, if no white man be at hand. We must conclude, therefore, that this immunity is principally due to the presence of some protective substances in the blood of the negro.

As regards mulattoes, the statement of La Roche to the effect that the least mixture of white blood with the black increases susceptibility, and that the danger is in proportion to the amount of white blood in the mixture, is borne out by experience.

The influence of *residence* in a yellow fever locality in diminishing the susceptibility of the white race is another remarkable feature in the history of the disease. It is only in very severe outbreaks that the white native is attacked, and this is even then, upon the whole, confined to white children, on the other hand, so long as they belong to the class of "newcomers," are liable to contract the infection, but they contract it in a very mild form.

Length of residence for a number of years in a town where yellow fever is endemic or frequently epidemic confers on the stranger, in a minor degree, the insusceptibility of the white native; but this holds good only for those who actually reside in the focus of infection. Those who dwell in the neighbouring country, or who take refuge there during epidemics, are nearly as liable as strangers to contract the disease if exposed to it. The length of residence necessary to afford protection will vary according to the frequency with which the infection appears in the place. Torres found that in Rio, where the disease is endemic, 66·7 per cent of the foreigners occurred in those whose residence was under a year; 10 per cent in those who had lived less than four years in the town, and only 4·2 per cent in those who had more than four years sojourn. These figures agree fairly well with those of Rey and Lota, and may be



taken as an approximate numerical statement of the ratio of susceptibility to length of residence. The duration of immunity, whether acquired by birth or residence, is in most cases lifelong, but not invariably so. It has happened that the native of a yellow fever locality who has lived for a number of years in a cold climate has had a fatal attack on returning to his native town. But apart from change of residence, the immunity of residence is not necessarily complete, so as to ensure safety in all circumstances. An individual may, indeed, live for years in an infected town, provided he inhabits a quarter not visited by the disease, without acquiring any real immunity; and, in this case, whether he goes abroad or stays at home he is liable to be seized during a severe epidemic. If the insusceptibility acquired by birth or residence were simply a matter of acclimatisation, those living in the immediate vicinity of an infected city should share in it equally with those who live within its limits; but this, as we have seen, is not the case. The immunity of the native, in its highest degree, is acquired by having passed through a mild form of the disease in infancy. The immunity of the stranger, who has resided for some years in a yellow fever town, is possibly the result of repeated inoculation of the virus in doses insufficient to give rise to a recognisable attack; and this view is rendered probable by the fact that during an epidemic many who escape the declared disease suffer from nausea, giddiness, headache, constipation, and yellowness of the skin, suggestive of an abortive form of the malady. Acclimatisation, properly so called, if these views are correct, plays a smaller part than is generally supposed in conferring protection on natives and strangers of the white race. But the fact that Europeans belonging to the south of Europe enjoy a relative advantage compared to the Scandinavian or Englishman indicates that climate has a certain influence on susceptibility. Pym remarked that the case-mortality in Gibraltar was very small among those men of the 10th Regiment who had been quartered for some years in the East Indies. Those who had recently joined the Regiment, on the contrary, suffered severely. Of eight officers who had been in the East Indies all recovered. Of seven who had not been in the East Indies, five died. The residence in a warm climate did not appear to diminish the liability to the infection, but reduced its fatality.

9. *Personal Conditions — Occupation.* — Cooks, bakers, blacksmiths, engineers in steamers, sugar manufacturers, brewers, and hatters have been observed to be particularly liable to suffer in exotic epidemics. These occupations do not appear to involve the same risk in the tropics; is it that the artificially heated atmosphere attracts mosquitoes in temperate climates to the workshop in which these trades are carried on? Instances are fairly numerous in which yellow fever is said to have appeared first in the houses of washerwomen engaged in washing clothes from infected vessels, but few of these are altogether free from doubt. Nothing is more conclusively proved by the experience of yellow fever hospitals than the immunity of those employed in washing the linen of the sick. Physicians have often paid a heavy tribute to this disease.

In Jamaica, in 1808, two assistant surgeons and twenty-one out of twenty-two hospital attendants were attacked. In Senegal, in 1830, of twelve physicians exposed, ten were attacked and six died, and in 1878, twenty-two out of twenty-seven perished. At Vera Cruz, in 1862, the orderlies in attendance on the sick suffered out of all proportion to the rest of the army, and had to be replaced by the Nubians who, as we have mentioned, proved refractory to the disease. Confessing priests, whose duties take them to infected houses, have always suffered greatly. In severe epidemics the attacks among this class of priests have varied from 80 to 98 per cent. Custom-house officers and labourers employed in discharging ships from yellow fever ports furnish a large proportion of victims.

*Age and Sex.*—In the Lisbon epidemic of 1857 it was ascertained that of 3466 deaths, 2061 were males and 1405 females. The age distribution per 1000 was as follows:—

Years—1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
26	116	212	194	166	152	94	31	9

These figures shew that yellow fever is more fatal to men than to women and to adults than to children. As it generally assumes a milder form in women than in men the ratio of liability of the latter will not be so great as that of the mortality.

*Remote Causes.*—Fraser informs us that, among the troops stationed at Gibraltar, it was observed that the hard drinkers and debilitated were those most severely affected. “Almost all the first victims at Baltimore in 1794 were persons habituated to the immoderate use of ardent spirits, and very few of them recovered.” Excesses of all kinds, fatigue, exposure to the sun’s rays, and depressing mental emotions are enumerated as entering into the causation of yellow fever.

*Second Attacks.*—One developed attack of the disease ensures immunity for life: exceptions to this rule are extremely rare. When yellow fever reappeared at Gibraltar in 1813 there were about 5000 persons within the walls who had already been affected. None of these, so far as could be ascertained, suffered a second attack. On the *Lombardia* (page 339) those who escaped were those who had already passed through the disease (13).

*Relapses* during convalescence, although not common, are full of danger. They are usually to be traced to indiscretions in diet or exposure to cold.

*Incubation.*—The period of latency in yellow fever usually extends from thirty-six hours to four or five days, but it may be prolonged to a fortnight.

*Transmission of the Virus—By baggage, clothing, and merchandise.*—The American Medical Commissions and the French Mission to Brazil concur in holding that yellow fever is not conveyed by fomites, and hence conclude that disinfection of articles of clothing, bedding, and merchandise is unnecessary. It has been proved that clothing, bedding,



etc., soiled with yellow fever discharges do not convey the infection, but it does not follow that the disease cannot be introduced into a locality by mosquitoes in baggage or some kinds of merchandise. Infected mosquitoes are probably more frequently transported in these ways than is generally supposed. As this is a question not only of scientific interest but of practical importance, I shall briefly state the grounds on which I dissent from the sweeping conclusion of these Commissions. Strain informs us that numerous cases of yellow fever had occurred prior to 1893, in St. Paulo, in persons who had contracted the disease elsewhere, but that it did not spread. From this we may safely conclude that the *stegomyia* was then absent from that locality. It was in 1893 that the disease first appeared among those who had never been out of the city, and in the following circumstances: A German had stored in the lobby of his house and in the small courtyard at its back, a number of cases containing pieces of machinery packed in straw. These came by rail from Santos, a port town fifty miles distant, where the disease was then raging. Within a few days of the opening of these cases, Strain was called to the son-in-law of this man, whom he found suffering from a moderate attack of yellow fever. In all, four cases occurred in this house—two being fatal. Next to be attacked was a cabinetmaker, whose workshop was built against the wall of the courtyard in which a number of the packing-cases were stored. From this as a centre the disease spread to other houses in the neighbourhood. It is difficult to avoid the conclusion that infected mosquitoes had, in this instance, been introduced from Santos along with the packing-cases. The fatal epidemic at Lisbon in 1857 originated in, and was for a time confined to, the custom-house (2, 11). The first victim was a man employed in a badly ventilated room in which the baggage from Brazil, where the disease was then prevailing, was examined and stored. Ten persons in succession employed in this store were attacked and nine died. Here was a clear case of house infection: but whence was the infection derived? Not from the presence in it of a yellow fever patient. The only admissible explanation, in the present state of our knowledge, is that the room was infected by mosquitoes introduced by baggage or goods from Rio. Another instance clearly pointing to the transmissibility of the infection by baggage is the Madrid outbreak of 1878 (7, 9). Some 17,000 Spanish troops returned from Cuba in the autumn of that year. No cases of fever occurred among them during the voyage or afterwards. They landed at Santander, and more than half of them proceeded direct to Madrid by rail, a distance of 300 miles, which would not occupy more than a day. The troops were disbanded and took up their quarters in and about Tetuan Street. It was here that yellow fever appeared about the 15th of September, not among the soldiers, but among the inhabitants of the quarters where they had taken up their abode. Cases continued to occur for a month. In all, about fifty were attacked and thirty-five died. How was the disease introduced? Not by the soldiers, who remained healthy. Not by mosquitoes infected on the spot, for

there was no source from which the infection could have been derived. No other explanation remains but that the infection was conveyed by the baggage of the soldiers, which was not disinfected before it was put on board or after being disembarked at Santander. We must either suppose that a colony of infected mosquitoes was transported from the ship in, or adhering to, the effects of the soldiers, or that the baggage contained the germs of some unknown phase in the life of the parasite. The difficulty in admitting that mosquitoes from the ship were the agents of infection will be lessened, if we remember that the contents of the hold were transferred bodily and directly, so to speak, to Madrid, and if infected mosquitoes were present in the hold, a number of them would have a fair chance of being conveyed by the baggage.

Instances of the infection being carried to isolated individuals by contaminated clothes and other effects are not numerous, but the following case recorded by Dr. Paterson appears to me conclusive. Bahia was free from yellow fever from September 1850 to March 1852. In the beginning of May 1851, the barque *Gipsy* arrived from Rio with the disease on board. The master of the vessel had already passed through the disease in the West Indies. His wife, who was on board, was immediately landed and went to reside a mile or so in the country. On the 16th of June, six weeks after landing, she was seized with yellow fever and very narrowly escaped with her life. She had not, in the meantime, been on board, nor did she have any communication with the vessel, except through her husband, who slept on shore and passed the day on board. He himself remained in perfect health all the time. The doctrine that clothes soiled with the discharges of yellow fever patients are innocuous is fully confirmed by experience, but it does not justify the conclusion that the infection cannot be conveyed in clothing, merchandise, and baggage.

*Possibility of other Modes of Transmission.*—The success which has followed measures directed to the extermination of the *stegomyia* furnishes the strongest evidence that the mosquito is the ordinary, and justifies the presumption that it is the sole agent of infection. Another argument in favour of the exclusive agency of the *stegomyia* in the transmission of yellow fever is found in the striking correspondence between the geographical distribution of yellow fever and that of the *stegomyia*. But, as the parasite of yellow fever and its life-history are unknown, the possibility of the infection being communicable in some other way cannot at present be altogether excluded, however improbable it may appear that a parasite which has become adapted to life alternately in man and the mosquito, should also be capable of an extra-corporal existence.

Does the mosquito hypothesis adequately explain all the well-ascertained facts in connexion with the propagation of the disease? If we were to accept the accounts of yellow fever appearing spontaneously at sea in vessels from cold latitudes, of its being communicated by clothing stowed away in boxes for three years or longer, of a physician contracting the disease in Paris while examining the dejecta of a yellow fever patient

obtained from abroad, and similar stories, the hypothesis would be entirely inadequate. Most of these narratives may be put aside as being not only improbable in themselves, but as defective in detail. There remain, however, a few cases sufficiently well attested, which, as they present certain difficulties—real or apparent—must be briefly noticed.

1. Béranger-Féraud, an unimpeachable authority, states that he knew an instance of yellow fever breaking out in a remote village of the Basses-Alpes, in the house of a family that had just received the non-disinfected clothing of a patient who had died of the disease in Senegal. If this outbreak had been witnessed by himself the narrative would have carried greater weight. He, however, believed it to be authentic.

2. Another case deserving notice is that of Dr. Chaillon who contracted the disease at the village of Montoir, some four miles from St. Nazaire, while attending three patients who had sickened on board the *Anne Marie* (13), to which reference has already been made, and who had gone home to their native villages. The doctor, who had not been near the town, was seized on the 8th or 9th day after commencing his attendance on these patients, and died with black vomit and all the symptoms of yellow fever. Dr. Chaillon must have received the infection directly from his patients or from the bite of an infected *stegomyia* conveyed from the ship in their effects. Those who attach any weight to the instances adduced above of the transport of mosquitoes in baggage, will see little difficulty in accepting the latter view, which justifies every precaution in respect to clothing.

3. The history of H.M.S. *Eclair* is interesting. This ill-fated vessel, which was infected at Sierra Leone in July 1845, introduced yellow fever into the island of Bona Vista and then carried it to England, where fatal cases continued to occur till the 11th of October. Out of 146 officers and men 140 were attacked and 73 died. After undergoing disinfection and extensive repairs in England, she sailed for the Cape under the name of the *Rosamond* on February 23, 1847. On entering warm latitudes, several cases, which were looked upon as yellow fever, appeared on board, one of which terminated fatally with black vomit. If these were cases of genuine yellow fever the infection must have persisted in the vessel for seventeen months from the date of the last case without the possibility of a fresh infection—a view which cannot well be reconciled with the mosquito hypothesis as now accepted.

4. The case of the U.S. ship of war *Plymouth* is of importance, as the facts are beyond dispute. The *Plymouth* was infected at Vera Cruz in the beginning of November 1878. She was fumigated with sulphur during her homeward voyage, and again after her arrival at Norfolk, and for a third time at Portsmouth, N.H. She then proceeded to Boston where she was dismantled, everything movable taken out of her, exposed for three months to a temperature about the freezing-point, and twice fumigated, first with 30, and again with 50 lbs. of sulphur, all openings being closed. On being refitted, she put to sea on the 15th March, and within a week two cases of yellow fever declared themselves on board.

The infected insects must, in this instance, have survived the cold and repeated disinfections for 130 days (21). The cases of the *Elan* and *Falmouth*, if they justify some reserve in concluding that the bite of an infected mosquito is the *sole*, do not touch the truth that it is the *ordinary* and *only known* mode in which the disease is communicated.

**Pathology and Morbid Anatomy** *Rigor mortis* appears early and is well marked. The yellow colouration of the skin, not always present during life, is rarely absent after death, and is usually associated with angulations and ecchymoses. The hands, feet, and genital organs are cyanosed.

The blood in yellow fever coagulates loosely, the fibrin being diminished. The number of the red corpuscles is not necessarily reduced nor the percentage of hæmoglobin they contain. The white corpuscles are diminished to a varying extent. In a case reported by an American Commission, the leucocytes fell from 6355 to 2666, and an entire absence of eosinophils was noted. Further observations are necessary to establish accurately the leucocytic formula of yellow fever. In two cases observed by Gray, the percentage of large mononuclears was 7.66 and 8.33 respectively. This increase, even if constant, a point not yet determined—is not so great as to cause it to be mistaken for malaria; besides, the large mononuclears of yellow fever are not pigmented. The yellow colour of the serum is due to free hæmoglobin.

**Brain and Cord.**—The more constant morbid alterations met with in the nerve centres are venous congestion of the meninges, and, to a less extent, of the substance of the brain and cord; and a turbid yellow effusion into the subarachnoid space and cerebral ventricles. Minute hæmorrhagic points are not infrequently observed in the pia mater and brain.

The *respiratory organs* in most cases seem normal. Occasionally, however, the lungs and bronchi are congested, and hæmorrhagic extravasations are occasionally met with in the lungs and beneath the pleura.

**Heart and Pericardium.** Usually no lesion is observable in the heart, if we except a dull and flabby appearance which this organ often presents in common with the muscular system generally. Minute ecchymoses, however, are sometimes met with in the muscular substance and under the endocardium. Effusions—serous, purulent, or sanguineous—are occasionally found in the pericardium, which may also be injected, or the seat of small petechial looking hæmorrhages. The cavities of the heart contain more or less loosely clotted or fluid blood. The right ventricle often contains pale-yellow coagulum.

**Stomach.**—Morbid alterations, more or less pronounced, are always met with in the stomach, whatever the period at which death occurs. More or less of a black fluid, similar to black vomit, is almost always present in the cavity. The mucous membrane is irregularly congested in patches or bands, most marked at the cardiac extremity. The rugæ are swollen and thrown into corrugations, so as to present the appearance of a mass of lumbrici the *boursouslement vermineux* of French authors.

The hyperæmia is less marked in patients who succumb at an advanced period of the disease. Larger or smaller ecchymotic points are to be distinguished in the congested areas. The mucous membrane is often softened and in places eroded.

Under the microscope, the superficial venules and capillaries are seen to be engorged, and undergoing fatty degeneration. The tubular glands are variously deformed and atrophied, and their epithelium is fatty. Minute hæmorrhagic foci are met with here and there between the glands. The submucous connective-tissue is comparatively intact; although here and there points of congestion may exist; and, according to Sternberg, an unusual number of leucocytes is occasionally to be met with in the submucous coat.

*Intestinal Canal.*—Black matter, similar to that found in the stomach, is often present in the upper part of the canal. The contents of the intestine usually give an acid reaction. Vascular arborisations, more or less extensive, are observed, especially towards the lower part of the ileum. The solitary glands, as well as Peyer's patches, are sometimes found enlarged, and fatty degeneration of Lieberkühn's crypts has been demonstrated.

The *liver*, which presents some shade of yellow, from dull chamois to a brownish-orange, is generally of normal consistence and volume. The cut surface is somewhat friable. On section, its substance usually presents an exsanguine appearance, but when death occurs early it may be found hyperæmic. The liver-cells, especially in the peripheral lobular zone, are seen to have undergone fatty degeneration, not, however, uniformly throughout the gland. Interstitial proliferation has been noticed by Babes and others. The state in which the gall-bladder is found varies—sometimes empty, at other times containing a small amount of dark bile of natural quality, or viscid, tarry, or mixed with blood.

The *spleen* is not enlarged nor altered in consistence, except as the result of previous malarial disease.

The *kidneys* are usually of normal size, and not congested to any extent, except when death has occurred within the first three or four days. Small hæmorrhages, however, are occasionally observed under the capsule, in the mucous membrane of the calices and pelves, and as pinpoint extravasations into the cortical substance. The renal epithelium undergoes cloudy swelling and fatty degeneration. The tubes in some places are divested of epithelium, and are often filled with a hyaline or granular albuminous material. The capillaries here, as in other organs, exhibit evidences of fatty degeneration. The bladder is usually contracted and empty.

**Symptoms and Course (General Sketch).**—In exceptional instances a certain degree of malaise, characterised by anorexia, constipation, headache or vertigo, is felt for a day or two before the attack. Much more frequently yellow fever declares itself abruptly, seizing the patient without warning while in his usual state of health.

The first symptom is usually a chill, which may amount merely to a



chill of coldness, so slight and evanescent as scarcely to attract attention, or it may be more intense, declaring itself by a rigor, severe but of short duration, or by repeated shiverings alternating with heats. In some cases the chill is absent. This stage of invasion generally lasts from two to twelve hours, and its intensity and duration are often observed to bear a direct relation to the severity of the impending attack. Severe frontal and ocular headache, racking pains in the loins and limbs, pallor of the skin, and a rise in the temperature, are the usual symptoms of the invasion stage.

As the chill passes off, the face becomes red and turgid, and the eyes injected, brilliant, and watery; the headache and the pains in the loins, joints, and muscles of the extremities—the *coup de barre* of French authors—increase in intensity. The patient is agitated and anxious; the mind usually remains clear, or at most wanders at night; less frequently there is active delirium. The temperature in the meantime rises rapidly, generally attaining its fastigium within twenty-four or thirty hours from the onset of the disease; and reaches some point between 103 and 107 F. according to the severity of the attack. The respiration is hurried and laborious, and the pulse accelerated, full, and bounding. The skin in the milder cases is moist, but in the severer forms it is dry and pungent. The appetite is lost; the tongue, often narrow and pointed, is covered with a white fur, the tip and edges being red. The bowels are constipated as a rule, but are sometimes relaxed; there is a sensation of heat, pain, or distress at the epigastrium, which is tender on pressure. The stomach becomes irritable, and vomiting of a clear acid fluid ensues. The urine is scanty, and from the second day is found to contain albumin, while the urea is diminished. On the second or third day seldom later than the fourth—a change takes place. The temperature and pulse fall; the headache and pains subside; the characteristic redness and turgidity of the face tone down, as does also the suffusion of the eyes, which in many cases now assume the yellow tinge which may afterwards extend to the rest of the body. The gastric irritability and distress likewise abate, and the patient feels better. This is the turning-point in the disease. If the improvement is to end in convalescence, the temperature falls gradually to the normal; the gastric distress disappears, the appetite returns; the urine increases in quantity, while the albumin steadily diminishes and a corresponding increase of the urea takes place. If, on the other hand, after a lull extending from a few hours to one or two days, the gastric symptoms reappear in an aggravated form, with thirst, anxiety at the præcordia, and vomiting of a clear liquid mixed with chocolate-coloured flakes, or of a fluid uniformly black, and depositing on standing a coffee-ground sediment, the patient's life hangs doubtfully in the balance. These symptoms are accompanied either by a persistence or recrudescence of the fever, or by a fall of the temperature below normal, which is still more ominous, and by a diminution of the urinary excretion, with a corresponding increase of albumin, which generally reaches its maximum from the fifth to

the seventh day. Even at this stage a change for the better may take place. In this case, the irritability of the stomach again subsides, the patient's strength rallies, a gradual amelioration of the other untoward symptoms follows, and convalescence is rapidly established. More frequently, however, the balance inclines the other way. The prostration increases, copious vomiting of black matter sets in; the yellowness of the skin becomes more pronounced and generalised; in the more malignant cases, the skin is likewise covered with petechiæ and vibices; and along with these, and depending upon the same conditions, hæmorrhages often take place from the mucous membranes. In some epidemics, gangrenous spots on the limbs or on the scrotum have been of relatively frequent occurrence. The tongue now becomes dry and brown. While these ominous symptoms are being evolved the mind may remain clear and continue so till the end. More frequently the patient, though not incoherent, is dull, confused, and apathetic; he fails to realise his condition; expresses himself hopefully as to his state; lapses from time to time into a dreamy reverie, or attempts to get out of bed. Occasionally there is active delirium. Towards the end hiccup sets in, the features become shrunken, subsultus tendinum appears, a clammy sweat breaks out in the skin, and the patient dies exhausted, comatose, or in convulsions.

**Grades and Forms.**—The most useful classification is that which recognises three grades of intensity—the mild, the severe, and the grave; and arranges anomalous forms separately under the heading of pernicious.

The distinctions between the mild, severe, and grave forms of yellow fever go deeper than mere differences in the danger they involve, and appear to be, in some way, related to the evolution of the morbid processes determined by the infection.

1. In mild yellow fever the initial paroxysm, coinciding with the presence of the virus in the blood, constitutes, so to speak, the whole disease. Charts 1 and 2 (p. 337) represent the common course of the fever, although in many cases the fall of the temperature begins as early as the second day.

2. The distinctive feature of the severe form is the evolution during the remission stage of the characteristic symptoms of the malady—jaundice, black vomit, hæmorrhages, anuria, mental and nervous disturbances, oppression of the respiration, and slowing of the pulse. Charts 4, 5, and 6 shew the more common thermometric types in this form.

3. In the grave form (Charts 7 and 8) the cortege of symptoms proper to the remission stage make their appearance within the first three or four days, that is, during the first stage. Symptoms referable to the nervous system especially come into prominence. The following brief notes will convey a more just idea of the symptoms and course of this dangerous form than a general description:—

1. B. S. 1st day. Trembling of extremities, headache, vomiting. 3rd day. Stupor, urine scanty, vomiting ceased. 5th day. Urine suppressed. The patient lingered on in a semi-conscious state till the seventh day of illness.



2. M. L. 2nd day. Violent headache, followed by stupor. 3rd day. Black vomit. 4th day. Features pinched, patient semi-conscious, black vomit, tarry stools, death.

3. D. L. 1st day. Fever, vomiting, constipation. 2nd day. Obstinate vomit, sometimes of a brown colour. 3rd day. Jaundice, tongue moist, no great thirst. 4th day. Black vomit. 5th day. Urine suppressed. Death on seventh day in the midst of general convulsions.

4. P. T. 1st day. Violent headache, great prostration. 2nd day. Eyes sunken, clammy sweats, cramps in legs and arms. 3rd day. Suppression of urine and chrium. Died on the seventh day comatose; no black vomit or jaundice throughout.

5. W. C. 1st day. Chill and headache. 2nd day. Agonising pain in back and spine; skin hot but moist, vomiting, constipation. 3rd day. Patient felt better, and said she would be able to get out to-morrow, although black vomit had already set in. Death on fourth day.

Some cases, which may be truly called malignant, run even a shorter course. The following, reported by a French physician, may be taken as an example of these:—

On the first day the patient's face was puffy and of a leaden colour. Skin cold, great thirst, some nausea, tongue clean but dusky. Complete absence of headache and *comp de barre*. In fact, the patient had no pains whatever. On the morning of the second day complained of heaviness of the head, great prostration, and constipation. In the afternoon there was severe pain in epigastrium, and black vomit set in. The stools were dark, and there were hæmorrhages from nose, gums, and tongue. On pressure blood oozed from the tongue as from a sponge. Towards evening delirium, stertorous respiration, and death within forty-eight hours.

The pernicious forms, on the other hand, are distinguished by the development of some special symptom or group of symptoms foreign to the ordinary phenomena of the disease. I shall restrict myself to the briefest notice of three of these:—

1. *The Apoplectic Form.* The patient is more or less suddenly struck down with vertigo followed by stupor, coma, and convulsions, generally terminating in death. The pulse is weak, and finally becomes faltering and irregular, the skin is cold and clammy, or dry and flabby; the pupils dilated, and the patient dies comatose.

2. *The Algid Form.*—This form was of rather frequent occurrence in the epidemic of Lisbon in 1857. The prostration is early and extreme, the features are sunken, the surface cold, and in severe cases this coldness extends to the lips, tongue, and breath. The temperature in the axilla often falls to 96° F. The pulse is small or imperceptible. In a large proportion of these cases the hæmorrhagic tendency is present in an extreme degree. Yellowness of the skin is often wanting, and, when it does appear, is generally limited to a slight yellow tinge of the conjunctive.

3. *The Choleraic Form.*—This form, which is rare, is marked by excessive

purging and vomiting, copious clammy perspirations, petechiæ scattered over the skin, and great prostration.

**Analysis of Symptoms.**—The *temperature* in yellow fever is marked by a sudden rise to  $104^{\circ}$  or  $105^{\circ}$  F. In rare cases it may reach  $109^{\circ}$  F. The fastigium is generally attained in twenty-four to thirty-six hours, and the temperature continues at this point, with slight variations, for a period of two or three days; sometimes longer. The further thermometric movements, varying according to the form of the disease, are indicated in the charts.

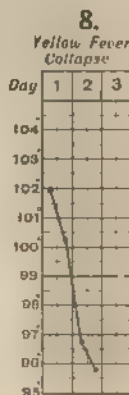
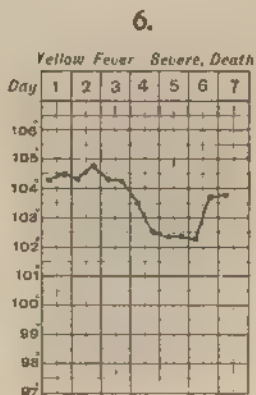
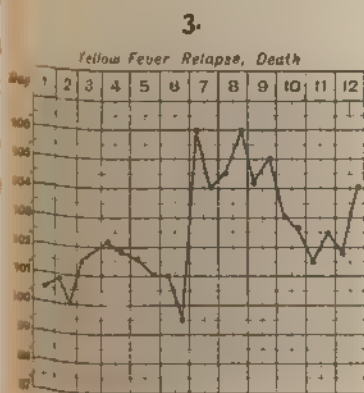
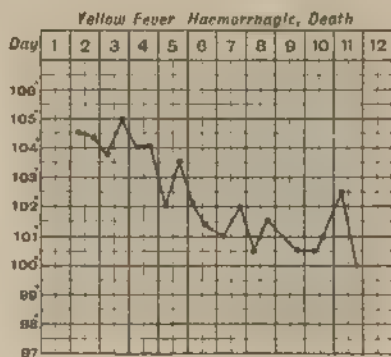
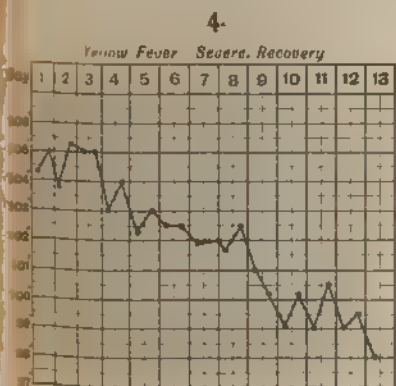
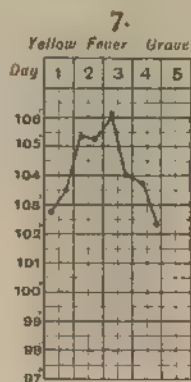
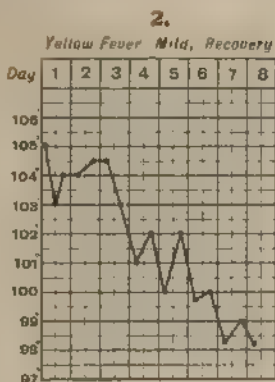
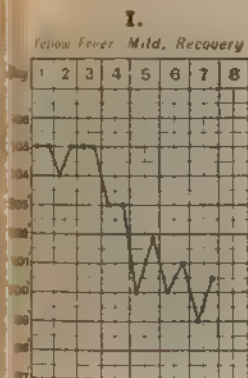
**Pulse.**—During the initial fever the pulse is accelerated, full, bounding, sometimes tense, at other times compressible; diminishing in force and frequency as the remission sets in. It often falls as low as 50—occasionally even to 40 per minute when the disease is severe. In grave cases it is small, feeble, accelerated, or slow, and towards the end irregular and intermittent. It may be observed that there is no correspondence between the number of pulsations and the height of the thermometer. The blood-pressure, at first above the normal, falls considerably during the stage of remission.

The *skin* is pale during the period of invasion, and when algid symptoms manifest themselves this state of pallor develops into lividity. When reaction is established the skin becomes hot and dry, or hot and moist. The face is now red and turgid, and the eyes suffused and brilliant. Yellowness of the skin is often absent in mild cases throughout the whole course of the disease; and, strange to say, it is often wanting in the algid form, even when hæmorrhages are present. It is rarely altogether absent in the other more intense grades of the disease although in these, too, it may be so little obtrusive as to be overlooked while in other instances the skin assumes a deep orange or even bronzed hue. Icterus seldom makes its appearance before the beginning of the remission, when the redness of the face has subsided. In some cases its advent is deferred until the approach of death, or it may not appear until after death. The yellowness is first noticed on the conjunctivæ and face spreads to the neck and chest, and then to the rest of the body.

Petechiæ and large irregular purpuric patches are met with especially in the algid and hæmorrhagic forms. An erythematous eruption on the scrotum, or around the vulva, is frequently observed; and, when present is looked upon as pathognomonic of yellow fever.

An altogether indescribable odour, exhaled from the skin in malignant cases, is a sure prognostic of death.

**Hæmorrhages** are occasionally, but seldom, seen in the early part of the pyrexial stage. They are of most frequent occurrence at a late period, that is, after the remission has set in; they are most extensive in the malignant forms, especially the algid, and are undoubtedly more common in some epidemics than in others. The most common form of hæmorrhage, of course, is the black vomit. Besides the purpuric spots and patches that are often the first signs of a hæmorrhagic tendency, we meet with bleeding from the nose, tongue, lips, and gums, from the whole



CHARTS 1-8.—Temperature Charts in Yellow Fever.

gastro-intestinal tract, from the uterus and vagina, from the bladder urethra, more rarely from the bronchial mucous membrane, and from ear and conjunctiva. Extravasations of blood may also take place the interior of the eye and destroy vision.

*White, Red, and Black Vomit.*—Vomiting is a very general symptom of yellow fever. It begins with the vomiting of an acid, colourless bile-tinged, and more or less viscid fluid; this may be distinguished as white vomit. The red vomit of Cunisset is simply gastric hæmorrhage; in this case the blood is expelled immediately after its escape from vessels, thus retaining its red colour. The vomiting of bright blood is justly looked upon as a dangerous symptom. Black vomit, which is its familiar name to the disease, usually makes its appearance during the period of remission. It is composed of altered blood, which, on standing, deposits a black sediment like coffee-grounds, the supernatant fluid being of a clear or slightly brownish colour. *Microscopically*, black vomit consists of glandular epithelium, red corpuscles, mucous cells, yellow pigment granules, fat-globules, granular debris, and various kinds of micro-organisms. Its chemical composition varies greatly. Its acidity is mainly due to hydrochloric acid. Cunisset in numerous analyses failed to detect in it urea, the biliary acids or salts, or cholesterin.

The *urine* is acid and high-coloured; its density is high, and varies according to the amount of albumin that it contains. The quantity voided, which is diminished from the onset of the disease, becomes still more scanty during the third stage; and in cases tending to a fatal issue complete suppression often occurs. Albumin makes its appearance during the febrile stage even in mild cases—the amount bearing a direct relation to the severity of the attack. The urea and chlorides are notably diminished, and the uric acid to a less extent. The urea, however, is not always decreased at the beginning of the fever. Bile is only present at the end of the fever. Blood is present when there is hæmorrhage from the kidney, bladder, or urethra.

*Stools.*—Constipation is the general rule during the febrile stage. In some epidemics bilious or choleraic diarrhœa has been of frequent occurrence. In favourable cases the bowels resume their normal action when the remission sets in. Obstinate constipation or diarrhœa and melæna are alike dangerous symptoms at this stage.

*Morbidity and Mortality.*—The morbidity and mortality in yellow fever vary extremely according to the intensity of the outbreak, the proportion of susceptible subjects in a population, and the hygienic conditions of a locality. The first outbreaks in Spain at the beginning of the nineteenth century were remarkable for the large proportion of the population attacked. The whole community was susceptible. Pym, who was an eye-witness of the epidemic of 1804 at Gibraltar, states that, of 14,000 souls constituting the civil population, he could only trace 12 individuals who escaped, and 12 of these had already passed through the disease. At Cadiz in 1800 there were 48,520 attacks and 7387 deaths in a population estimated at 57,499. At Seville, in the same year, the

were 76,488 attacks and 14,685 deaths in a population estimated at 80,568. No great accuracy need be claimed for these figures, but they suffice to show the wide diffusion which yellow fever may assume in a susceptible population. The disease never attains the same prevalence where yellow fever is endemic.

The case mortality may be said to range from 12 to 80 per cent. In Rio it reached 94.5 per cent in 1898. It has been known to be as low as one-half per cent. In cities where the disease is endemic or recurs at frequent intervals the majority of adults are insusceptible, and thus a large proportion of attacks will fall on children, who take the disease in a mild form, hence the total and case-mortality will be correspondingly low. Taking the statistics of the Martinique hospitals from 1819 to 1869 as a guide, we may reckon the average case-mortality of Europeans in the West Indies at 23 per cent. It is interesting to observe that non-propagable outbreaks in high latitudes are almost uniformly very fatal. At Marseilles, in 1823, the case-mortality was 60 per cent., at St. Nazaire, in 1861, 59 per cent.; at Swansea, in 1865, 60 per cent. Is this due to the length of time that has elapsed between the infection of the mosquito and the inoculation of the virus? Yellow fever is generally of a more malignant type in the shore districts of an infected town, becoming less prevalent and also less fatal as we recede from the focus of infection. This is, no doubt, to be ascribed largely to the unfavourable circumstances and dissipated habits of the population of these localities, but is also partly due to their being exposed to the risk of multiple inoculations of the virus in places where the *stegomyia* abounds.

**Diagnosis.**—A fever of a single paroxysm, accompanied by congestion of the face, injection of the eyes, severe lumbar pains, gastric irritability, albuminous urine, black vomit, and other hæmorrhages cannot well be mistaken for anything else than yellow fever. The complex of symptoms when well marked is pathognomonic. But in the early stage, before the more characteristic symptoms develop, the diagnosis is not always easy. Attention should be paid to collateral circumstances, such as the geographical limits within which yellow fever prevails; its predilection for seaports, its epidemic character, and the special liability of newcomers. It is a safe rule to regard with suspicion any fever occurring in a European recently arrived in a place where yellow fever prevails. Neglect of this rule has led to disastrous results. The Italian war-vessel *Lombardia* (13) was lying in the harbour of Rio in 1896 when yellow fever was prevalent on shore. One of the men who had landed was taken ill. The diagnosis of scarlet fever was made on account of the redness of the face and neck, and no precautions were taken. Twelve days later yellow fever began to spread on board, and out of 249 officers and men 242 were attacked, and 134 died. The 7 who escaped had already passed through the disease.

The diseases most liable to be mistaken for yellow fever are: the bilious remittent form of malaria often found in fresh arrivals,



blackwater fever, and relapsing fever. In malarial bilious remission the vomiting is more distinctly bilious than in yellow fever. Albuminuria is rare. There is pain and tenderness in the splenic region at the beginning, followed in a few days by enlargement. The presence of the malaria parasite and of pigmented leucocytes in the blood will establish the diagnosis. Blackwater fever is not a disease of newcomers but of those who have been for a year or more in the tropics. It is confirmed from the spectroscopic evidence of hæmoglobin, not always available. The porter colour of the urine, its separation on standing into two layers, the upper clear and of a port-wine colour, and a sedimentary layer consisting of epithelium, hyaline and granular casts, and yellowish-red pigment masses, and the pink tinge of the froth on being shaken will settle the diagnosis (*cf.* p. 299). The increase of large mononuclears bearing the characteristic change of ment will be confirmatory, if confirmation be required. Relapsing fever is often accompanied by jaundice, vomiting, severe lumbar pains, and occasionally even by black vomit. Here, again, the collateral circumstances already mentioned should be taken into account. Albumin is very rarely present in the urine of relapsing fever. The enlargement of the spleen, the distinct leucocytosis, the relative increase of polymorphonuclears, and the presence of the *Spirillum obermeieri* will suffice to establish the diagnosis.

The prognosis in yellow fever must always be guarded, as unfavourable symptoms may appear when least expected. If the temperature in the first stage be moderate, the skin moist or covered with perspiration, and if the temperature begin to fall early and reach the normal, without any symptoms of depression; if the epigastric distress and irritation be slight and disappear with fever; if the urine be in fair quantity, contain little albumin, and a moderate amount of urea, the prognosis is favourable.

If, on the one hand, the disease be ushered in by convulsions or spasms and long-continued chills; if the temperature rise to or above 106° F. or if, on the other hand, reaction be not at all or only imperfectly established, and algidity supervene; if the albumin in the urine increase while the urea diminishes; if generalised hæmorrhages, petechiæ, and purpuric patches make their appearance, and coffee-ground vomiting be urgent; finally, if delirium, vertigo, coma, or hiccup set in, an unfavourable issue may be feared. Perhaps the most dangerous of all symptoms is algidity with hæmorrhages. Scarcely any die of yellow fever; few, if any, recover from the grave form.

**Prophylaxis.**—The breeding-places of the stegomyia, which abound in the low-lying districts of seaports, claim our first attention. Permanent and temporary collections of water should be drained, and inequalities of the ground filled up, so as to afford a ready discharge for rain-water. When ponds cannot be dealt with in this way, petroleum should be spread over the surface to destroy the larvæ. Gutters must be kept in good repair, and swept out daily, to prevent stagnation. The courts and of dwelling-houses, especially in the poorer localities, afford cond

favourable to the multiplication of the stegomyia, which is essentially a domestic insect. Waste water from pipes and rain-water form, as I have often seen, permanent puddles in the dilapidated pavements of courts. Broken bottles, empty cans, barrels, and other household utensils provide receptacles for water, which are utilised by the stegomyia for depositing its eggs. These sources of mischief should be seen to and remedied. Cisterns and water tanks should be covered with gauze. In short, all the means of preventing the multiplication of anopheles should be adopted in the case of the stegomyia, and carried out systematically and persistently (*vide* p. 285).

The next point is to prevent the infection of the mosquito. The yellow fever patient should be removed at once to hospital, and his bed surrounded with mosquito netting. The sooner this is done the better, for it is during the first three or four days of the illness that the patient is a source of infection. The infected house and the adjoining houses should now be thoroughly disinfected. Sulphur dioxide, as Rosenau has shown, is "unsurpassed as an insecticide, having surprising powers of penetrating through clothing and fabrics, and killing mosquitoes even when hidden under four layers of towellings." Sulphur,  $1\frac{1}{2}$  lbs. for every 1000 cubic feet of space, is sufficient to disinfect a room thoroughly; and the sulphur method has this advantage that the substance is everywhere procurable, and requires no special apparatus for its application. When the patient cannot be removed from the room, it should be fumigated with insect powder (pyrethrum, 2 lbs. per 1000 cubic feet) and the stupefied gnats collected and burned.

Although bedding and clothing soiled with the discharges of yellow fever patients are innocuous, prudence suggests that they should be destroyed, if for no other reason than that they may harbour infected mosquitoes.

Ships in infected ports should anchor at as great a distance as possible from the shore and from infected ships, and to the windward of them; the crews and passengers should not be permitted to go on shore more than is absolutely necessary, and never after sundown. The young stegomyias, which bite by day, are rarely infected. Tanks, barrels, troughs, etc., containing water must be protected. In case of an outbreak on board, the method of disinfection already detailed should be employed. Not only the particular cabin in which the disease occurred, but all the rooms in that part of the vessel, should be fumigated. The vessel, if at sea should be steered for cold latitudes. Before opening the hatches of an infected ship, sulphur dioxide should be introduced into the hold until thoroughly disinfected a vessel that has had yellow fever on board should not be allowed to approach near the shore or other vessels.

Individual prophylaxis requires the avoidance of infected towns, houses, or ships. There is no good reason for excluding the influence of fatigue, exposure to the sun, and excesses as disposing to yellow fever. We know that these circumstances have an important influence in increasing the risk of infection in the case of malaria, and although too



much stress has been laid on the action of disposing causes in determining yellow fever, sobriety, a regular course of life, the avoidance of exertion and of exposure to the sun should be insisted on. Arsenic was used as a prophylactic in the epidemic of 1905 at New Orleans without any evident advantage.

**Treatment.**—The discovery of the agency of the *stegomyia* in the transmission of yellow fever has placed the prophylaxis of the disease on a secure basis, but has left us exactly where we were in respect to treatment, which remains empirical, and to a large extent directed to the symptomatic indications. In all cases it is important to have the patient removed from the focus of infection, and treated in a well-ventilated room. In the milder forms little more will be necessary than the administration of a hot mustard foot-bath and a purgative. When the temperature is moderate, the skin moist, and irritability of the stomach absent or trifling, a meddling line of treatment is to be avoided. In all cases—severe as well as mild—the hot mustard foot-bath is employed on the invasion of the disease, and repeated once or oftener according to circumstances. Its use favours diaphoresis, and tends to relieve internal congestions. The administration of a laxative or cathartic, as soon as reaction has set in, is also useful alike in mild and severe cases. This treatment is indicated by the constipation which is generally present, and justified by the good effect which the concurrent testimony of physicians, past and present, concede to it. As to the purgative adapted for this purpose there is less agreement. Castor oil has obtained the greatest number of supporters; it is best given in capsules or in the form of emulsion. The great objection to its use is its tendency to give rise to vomiting. When there is much nausea, calomel, in a dose of 5 to 10 grains, is preferable, and may be followed, if necessary, by sulphate of sodium, and the laxative action maintained by fluid magnesia.

When the temperature is high and the skin dry and hot, it is evidently desirable, if possible, to abate the febrile excitement. Quinine has been largely employed for this purpose; but experience has, upon the whole, decided against its utility at any stage of the disease. Antipyretics have been recommended, but should only be employed in the early stages of the disease and when the fever is high. It is contra-indicated when the heart's action is weak and the vital powers depressed. The camphor saline mixture, containing acetate of ammonium, nitrate of potassium, and spirit of nitrous ether, is of service in cases of moderate intensity; it reduces the temperature to some extent, and promotes the action of the skin and kidneys. When there is great arterial excitement, 5 to 10 drops of tinctura veratri viridis may advantageously be added to the mixture. The Brazilian physicians, according to Key, make use of a mixture containing infusion of jaborandi, acetate of ammonium, and tincture of aconite. When the *calor mordicans* is well marked such a combination seems indicated. It is said almost always to give rise to profuse diaphoresis and a fall of temperature.

Whatever may be the internal treatment adopted to assuage the

action, its efficacy will be promoted by systematic sponging of the body with cold or tepid water, and the assiduous application of cloths dipped in iced water to the head. The whole body—extremities and trunk—should be sponged or swabbed with a wet towel loosely wrung out of cold water, each part being dried and covered before proceeding to another. These spongings should be repeated every two or three hours, ice being added to the water when the skin is hot and dry, while cold compresses or ice are applied to the head. When the skin is moist and the temperature moderate tepid spongings are to be employed. Hyperæmia, which, however, is not common in yellow fever, should be treated with the cold bath. When the patient falls into an algid state warm baths may be of service.

A very important indication is to maintain the action of the kidneys. Effervescent alkaline drinks, when tolerated by the stomach, are the best means of obviating the danger from scanty excretion or suppression of urine. Vichy water (Celestine spring) generally answers well. If not procurable 60 grains of bicarbonate of soda to a litre of water charged with carbonic acid may be substituted. These alkaline drinks should be given in such doses as the stomach can bear. As a rule, small quantities, ice-cold, and frequently repeated, are better borne than large draughts, but the more taken within the twenty-four hours the better. If the stomach reject fluids and the urine be scanty, cold enemata should be resorted to. Water containing a teaspoonful each of common salt and bicarbonate of soda to a litre may be used, the amount injected should not exceed what the bowel can retain and absorb. By the assiduous use of cold or tepid spongings and of alkaline diluents the temperature is lowered, gastric irritability diminished, and the excretion of urine increased.

Some symptoms of frequent occurrence during the remission stage require special treatment.

*Heart failure*, indicated by a feeble irregular pulse, whether increased in frequency or abnormally slow, calls for hypodermic injections of ether, and the administration of strychnine in small and frequently repeated doses. Digitalis may also be found useful in this condition.

*Vomiting* is one of the most troublesome and intractable symptoms, for the relief of which all sorts of remedies have been tried, each seemingly serviceable in one case, and useless in another. Chloroform, 2 or 3 drops frequently repeated, is sometimes found to exercise a sedative effect on the stomach. Blair, who had a large experience of the disease, found drop doses of creosote in mucilage and sugar to be most generally beneficial. Nitrate of silver, in doses of  $\frac{1}{8}$  to  $\frac{1}{3}$  of a grain, alone or combined with opium, occasionally proves useful. Opium, however, should never be given except in small doses, and is absolutely contra-indicated when the brain is affected. Oil of turpentine, in 10 to 20 drop doses, given every two hours, has had numerous advocates, but experience respecting its value is very conflicting. Lime water, given with equal quantities of fresh milk, has a marked sedative action in many cases, even after black vomit has made its appearance. An ice-bag

applied over the pit of the stomach, and morsels of ice frequently swallowed, often give relief. Blisters were formerly much in use, but they seldom do good and occasionally become the source of uncontrollable bleeding, and should, therefore, be avoided. Sinapisms are not open to this objection, but they do not often prove of much service.

*Hæmorrhages* are symptomatic of an intoxication which tends to a fatal issue, even when the bleeding has ceased spontaneously or been checked by treatment; but as hæmorrhages manifestly lessen the patient's chance of struggling through the disease, some effort, however unpromising, must be made to arrest them. Gallic acid has frequently been tried, but not with encouraging results. More good has been obtained from the use of the tincture of the perchloride of iron in full and frequent doses, although this, too, more frequently fails. This remedy was found to give the best results in the Lisbon outbreak in which hæmorrhages were a prominent symptom. Ergotin certainly succeeds in some instances. In the case of epistaxis (Chart 5) recorded by Sternberg, ergotin, given by hypodermic injection, arrested the hæmorrhage without, however, preventing a fatal termination. Chloride of calcium deserves a trial. Nitrate of silver, perchloride of iron, and other astringents have been applied locally to control hæmorrhage from the gums and mouth. Adrenalin chloride would appear to be a useful local hæmostatic.

*Suppression of Urine* is one of the most formidable symptoms in yellow fever. Much may be done to prevent, but little to cure it. Dry cupping over the kidneys, fomentations, and hot packs are the least hopeful remedies.

A mode of treatment recommended by Sternberg has been most favourably reported on by a number of physicians who have had an opportunity of testing it. He gives hourly three tablespoonfuls of a mixture containing 150 grains of bicarbonate of soda and one-third of a grain of perchloride of mercury in 40 ounces of ice-cold water. This treatment does not interfere with the employment of the means we have recommended for reducing the temperature and maintaining the action of the kidneys, and should, I think, be adopted in all but the mildest cases.

*Alimentation.*—For the first two or three days the patient is better without food. If some support seems necessary, a little milk and lime water may be given occasionally. When the remission stage has set in and is progressing favourably, milk and lime water can be given for a day or two, and then, as convalescence proceeds, small quantities of chicken-broth may be allowed, and a return to solid food cautiously made. The greatest difficulties are encountered when vomiting persists or returns during the remission stage. Here again milk and lime water should be tried, and supplemented, or replaced if necessary, by nutritive enemata.

Stimulants should be altogether avoided, both during the febrile stage and the remission stage when convalescence is progressing satisfactorily. When bad symptoms appear during the remission, and the

heart's action and the patient's strength begin to fail, alcoholic stimulants are absolutely necessary. Iced champagne is generally recommended, but it cannot always be had, nor does it always agree with the patient. In these circumstances, one or two tea spoonfuls of good whisky or brandy should be given in half an ounce of iced soda-water. The amount and frequency of the dose is to be regulated by the condition of the patient, the way in which it is tolerated, and its observed effects.

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A. D.

#### DENGUE

By SIR PATRICK MANSON, K.C.M.G., M.D., LL.D., F.R.S.

**ONYMS.**—*Dengue* (derived, according to Hirsch, from the Spanish equivalent of the English word "dandy"; according to Corre, from some Hindustani word possibly *dangui*); *dandy fever*; *polka fever* (Brazilian); *three days' fever*; *bouquet* (corrupted *bucket*), on account of the eruption, *quassé* or *stiff-necked fever*; *exanthema arthrosia*, *rheumatismus febrilis rheumaticus*, *scarlatina rheumatica*; *plantaria*. These are but a few of the many more or less fantastic names which, from time to time, have been given to this disease.

**Definition.**—A specific infectious fever peculiar to warm climates. Occurring usually in widespread epidemics, it extends with great rapidity, and attacks a very large proportion of the inhabitants of the affected areas. Individual attacks are characterised by suddenness of onset; rapidly developed, quickly subsiding fever; intense headache and loin-ache; severe rheumatoid pains in or about joints and muscles; an initial erythematous and a terminal rubeoloid eruption, and a very low mortality.

**History and Geographical Distribution.**—Being almost entirely confined to tropical countries, rarely visiting Europe, and having but an insignificant mortality, we cannot wonder that, although very probably this disease has existed for ages, there are no records from ancient times which we are justified in regarding as applicable to dengue. Nor, for similar reasons, is it at all likely that the records available for the medical historian suffice to complete the list of the epidemic and local outbreaks even of later times since the specific features of the disease were definitely formulated.

The first recognisable descriptions of what must have been epidemic dengue refer to 1779; in that year we have trustworthy accounts of its occurrence in Cairo and also in Batavia. It would appear that these particular outbreaks were only a part of what, so far as regards tropical and subtropical countries, was a vast pandemic wave; for in that and the following years we hear of a disease, apparently the same, in places so far apart as India (1780), Philadelphia (1780), and Spain (1784-88). With the exception of a limited outbreak at Lima in 1818 we do not again hear of dengue until 1824. In that year, and in 1825, it was again extensively epidemic in India and at Suez; and from 1826 to 1828 it prevailed in the western hemisphere in the Southern States of the Union, in Mexico, in the West India Islands, and in the north of South America. From that time, and for nearly twenty years, we only hear of scattered and local epidemics about the Arabian coast (1835), in Calcutta (1836 and 1844), Bermuda (1837), Cairo (1845), Cawnpore (1847), and Senegambia (1845-48). From 1845 to 1849 it was epidemic in Brazil. In 1850-54 it spread to the United States and the West Indies, while about the same time (1853-54) a similar epidemic passed over India. In 1870-75 a fresh epidemic wave, starting apparently from the east coast of Africa in the neighbourhood of Zanzibar, spread all over the tropical parts of the eastern hemisphere. In 1872 it reached China, where, at Amoy, during the months of August and September, I had an opportunity of becoming practically acquainted with the disease. There appears to have been a corresponding but more limited epidemic in America confined to Louisiana. Minor epidemics occurred in Tripoli in 1878, on the Caribbean coast of North America in 1880, in New Caledonia in 1884-85, in Fiji in 1885, and in Tripoli in 1887. One of the latest and best recorded epidemics is that described by du Brun, which in 1888 and 1889 spread all over Syria, Asia Minor, and the Aegean shores of Greece and Turkey. Within the last few years dengue has



once more appeared in the Far East in epidemic form, extending as far south as Brisbane, Australia, where important studies of the disease have been made by Bancroft, Hare, and others.

From a study of the dates of occurrence of these various epidemics it would seem that this disease tends to assume pandemic characters once in about every twenty years. Independently, however, of the great outbreaks many minor epidemics occur in the intervals: moreover, it is asserted by some authorities that after epidemic visitations dengue tends to become permanently established as an endemic disease in certain countries where, as it is supposed, it was formerly unknown. Thus, it is said to have become endemic in Egypt since 1845; in Tripoli since 1855; in Cyprus and on the Syrian coast since 1861. As an endemic disease it is believed that dengue is more common in the West Indies than elsewhere.

Besides the countries already referred to, dengue is met with from time to time in the islands of the Pacific—Tahiti and the Hawaiian group, for example; and also on its eastern shores, as at Callao and Lima.

Speaking generally, therefore, its ordinary limit of diffusion may be set down as lying between 32° 47' N. (Charleston in South Carolina and Lodi in India), and 23° 23' S. (San Paulo in Brazil), but occasionally during warm weather it may spread farther north to 36° 10' (south of Spain), 39° 06' (Philadelphia), and even to 42° N. (the southern shores of the Black Sea).

**Characteristics and Spread of Dengue Epidemics.** The most remarkable feature about epidemic dengue is the rapid way in which it spreads through a community, and the large proportion of individuals it attacks. So rapid is its diffusion that it may be described as bursting upon a place. Both in suddenness of epidemic rise and in the large numbers attacked it is comparable to influenza. In regard to the latter feature—the numbers attacked—we find that in most epidemics hardly any one is spared; all ages, both sexes, all races, and every condition of life are affected indiscriminately. Seventy-five per cent, therefore, is not too liberal an estimate of the proportion of the population attacked during an epidemic outbreak.

The epidemic which I witnessed in Amoy in 1872 was no exception in these respects to the general rule. About the first week in August cases of an unfamiliar disease were reported in the town: by the end of the second week such cases were numerous, whole families being prostrated by it at a time; a week later such cases were still more common; and by the end of the month so numerous were the invalids that the business of the town was seriously interfered with. All the patients and attendants in the native hospital were attacked one after the other. By the end of the following month, that is, about eight weeks from the incidence of the epidemic, all those susceptible in the town of Amoy had passed through the disease. The epidemic hung about the place for a month or two longer, being kept alive, apparently, by strangers from such neighbouring

towns and villages as had hitherto escaped the visitation. This seems to be the course of all dengue epidemics.

Like other infectious epidemic diseases, dengue tends to advance along the trade routes and lines of communication. Thus the epidemic of 1870-73, starting from Zanzibar, first reached Aden; from this port it was diffused north to the Red Sea coast and to Port Said, and east to Bombay, Calcutta, and Madras, whence it radiated all over India. Passing to Singapore it followed the trade routes south to the islands of the Eastern Archipelago, and north to Siam, Cochin China, and China. From India it was carried by coolie immigrants to Mauritius and Réunion in 1873.

**Influence of Climate, Season, Temperature, and Altitude.**—When dengue spreads beyond its ordinary geographical limits—as, for example, in the case of the epidemics in Philadelphia, Spain, Syria, etc.—these extensions occur only during the hottest part of the year, in late summer and early autumn. Hitherto such epidemics have been arrested by the approach of winter. Even when occurring within what may be designated as its normal geographical limits, dengue prevails principally, although not invariably, during the hottest part of the year. High temperature, therefore, seems to be one of the conditions it demands.

Epidemics occur indifferently during either the dry or the rainy seasons. The hygrometric condition of the atmosphere is therefore without a manifest influence on the disease.

It would appear that dengue, like yellow fever, prefers the coast line and the deltas and valleys of the great rivers, to the interior of continents: although to this rule, just as in the case of yellow fever, there have been exceptions; such as the epidemic of 1870-73, which spread all over India. Distribution and concentration of population on the seaboard and along rivers, and the freedom of communication between communities so placed, may have some influence in determining this clinging of the disease to such localities.

As a rule, elevated places enjoy at all events a relative immunity; if the disease be introduced into such localities, usually it does not spread. To this, again, there are exceptions, for the Syrian epidemic prevailed in places from 4000 to 5000 feet above the sea-level as well as on the coast.

There are no facts, therefore, to associate the diffusion of epidemic dengue with meteorological conditions other than that of high temperature. Nor does it appear to be influenced in any way by the mineral or hygrometric character of the soil.

High temperature, a certain density of a susceptible population unprotected by the immunity conferred by a recent epidemic, and the diffusion of a specific germ by human intercourse seem to be conditions necessary for the establishment of epidemic dengue.

**Symptoms and Course.**—An attack of dengue may be preceded for a few hours by feelings of malaise; or perhaps painful rheumatic-like twinges in a limb, finger, toe, or joint may herald its approach. Usually,



however, the disease sets in quite suddenly. A patient, describing his experience in this respect, said that in the morning he got up as usual, feeling quite well, and began to dress, but before he could complete his toilet he was so prostrated by pain and fever that further exertion was impossible, and he had to crawl back to bed. Similar stories, illustrative of the suddenness of incidence of the symptoms, circulate during every epidemic of dengue. Sometimes the fever is ushered in by a feeling of chilliness, or even by a smart rigor; sometimes a deep flushing of the face is the first thing remarked.

\* However it may begin, fever rapidly increases; the head and eyeballs quickly begin to ache excessively, and some limb or joint, or even the whole body, is racked with peculiar, stiff, rheumatic like pains which, as the patient soon discovers, are much aggravated by movement. The joints are the seat of great discomfort, amounting in some cases to actual pain. The face—particularly the lower part of the forehead, around the eyes, and over the malar bones—becomes suffused of a deep purple colour, and often the skin over part or the whole of the body, and all visible mucous membranes, are more or less flushed, the mouth and throat becoming sore from congestion and from small superficial ulcers. The eyes are usually much injected; very often the whole face is bloated and swollen. This congested, erythematous state of skin constitutes the so-called "initial rash."

These symptoms becoming in severe cases rapidly intensified, the patient in a few hours is completely prostrated; his pulse has risen to 120 or more, his temperature to 103, in some cases to 105, or even 106 F.: he is unable to move owing to the intense headache, the severity of the pains in limbs and loins, and the sense of febrile prostration. The skin, for the most part hot and dry, may be moistened from time to time with an abortive perspiration. Gastric oppression is apt to be urgent, and vomiting may occur. Gradually the tongue acquires a moist, creamy fur, which, as the fever progresses, tends to become dry and yellow.

In this condition the patient may continue from one to three or four days, the fever declining somewhat after the first day. In the vast majority of cases this, the first and most acute stage, is abruptly terminated about the end of the second day by crisis with diaphoresis, diarrhoea, dysuria, or epistaxis. When epistaxis occurs the relief to the headache is great and immediate. On the occurrence of crisis the erythematous condition of the skin rapidly subsides, if it have not already disappeared. In some cases crisis does not occur, but the fever slowly declines during three or four days. Thus the urgent symptoms for a time abate, and the patient rapidly or slowly passes from what in many cases may be described as the agony of the first stage to the comparative comfort of the second.

When the second stage is thoroughly established, and the temperature has sunk to normal, the patient is usually sufficiently well to leave his bed or even to attend to business. An occasional twinge in the leg, arm or finger, or a tenderness in the soles of the feet, and

perhaps giddiness in walking, may remind him of what he has gone through and warn him that he is not yet quite well. But the tongue cleans, appetite returns to some extent, and he feels moderately comfortable.

This state of matters continues to the fourth, fifth, sixth, or even to the seventh day, counting from the commencement of the illness. Then there is generally a return of fever, slight in most cases, more severe in others, and usually of very short duration—a few hours perhaps. Sometimes this secondary fever does not occur; very often it is overlooked. With the return of fever an eruption of a roseolar character appears. Along with the fever and with this “terminal eruption” the pains return, perhaps with more than their original severity. The fever subsides in a few hours, but the eruption, though at times very evanescent, may keep out for two or three days, being very generally followed by an imperfect desquamation. It seldom happens that the fever or pains of this stage keep the patient in bed, although that is the best place for him if a comfortable and speedy convalescence be desired. Rarely does the thermometer rise to  $103^{\circ}$  F.; it falls rapidly below the normal on the setting in of diaphoresis, diarrhoea, or other form of crisis.

The terminal eruption possesses very definite characters. It is absent in a very few only; it is quite possible that in many of those cases in which it was supposed to be absent it was slight and had been overlooked. As stated, it is roseolar in character, and usually commences on the palms and backs of the hands, extending for a short distance up the forearms. Its development is often associated with sensations of pricking and tingling. On the palms of the hands the spots are at first about the size of a small pea, circular, dusky red, and sometimes slightly elevated: they are best seen, however, on the back, the chest, upper arms, and thighs. In these situations they appear at first as isolated, slightly elevated, circular, reddish-brown, rubeoloid spots from one-eighth to one-half of an inch in diameter, thickly scattered over the surface; each spot being isolated and surrounded by normal skin. After a time the spots enlarging may coalesce in places; thus irregular, red patches, from one to three inches in diameter, are formed. Or perhaps there is a general coalescence of spots, isolating here and there patches of sound skin; in this case the islands of normal skin give rise at first sight to the false impression that they constitute the eruption—a pale eruption on a scarlet ground. In a few instances, indeed, the whole integument may be one unbroken, continuous sheet of red. The rash is usually most profuse on the hands, wrists, elbows and knees, and generally coalesces in these situations; where it may often be detected when absent or scanty elsewhere. The spots disappear on pressure; they never become petechial, or only in very rare cases. They fade in the order in which they appear: first on the hands and wrists, then on the neck, face, thighs and body, and last of all on the legs and feet. Desquamation may go on for two or three weeks. In many it is trifling in amount; for the most part it is furfuraceous; rarely the epidermis peels

off in flakes of any magnitude, and never in the broad sheets seen after scarlatina; often, for a day or two, it is accompanied with intense irritation.

In some instances the disease may be said to finish its course with the fading of the terminal eruption. Appetite and strength gradually return, and the patient, after a few days of debility, feels quite well again and able for work. But with many, indeed with most patients, their troubles do not end so soon. For days or weeks some muscle, tendon, or joint is the seat of the peculiar pains, which may become so severe as to send their victim back to bed again. Sometimes, three or four weeks after all apparent trace of the disease has vanished, a joint or a muscle will be suddenly disabled by an attack of this description. This may occur in patients who during the acute stage suffered perhaps little or no pain. A finger, or toe, or a joint of a finger or toe, may alone suffer. Of the joints perhaps the knee is most frequently affected, but wrists or shoulders also are often attacked; and the associated muscles may even undergo considerable atrophy from enforced disuse. The soles of the feet, too, and the tarsal articulations are favourite sites. The pains of dengue, both those occurring during the initial fever, and those which may be regarded as sequels, are difficult to locate with precision; the joints or muscle affected may be percussed, pressed, or moved with impunity. Du Brun locates those associated with the knee in the thigh muscles, which, he says, are painful on deep pressure. The pains usually are worst on getting out of bed in the morning, and on moving the affected part after it has rested for some time. They are relieved somewhat by rest and warmth. Passive movements are not painful, but any resistance to the movements of a limb may cause acute suffering. When a muscle is affected the pain is accompanied by a sense of powerlessness.

Convalescence may be very much delayed by the persistence of the pains, by anorexia, general debility, sleeplessness, evanescent feverish attacks, boils, urticarial, lichenoid, and papular eruptions, and by troublesome pruritus. Among sequels and complications may be mentioned enlargement of the lymphatic glands, particularly the superficial cervical; orchitis, possibly endo- and pericarditis, hyperpyrexia, and hæmorrhages from the mouth, nose, bowel, or uterus. Miscarriage is rare. The urine sometimes contains a trace of albumin, but nephritis does not occur.

Such, briefly, is a description of the dengue observed by myself in Amoy in 1872. It would appear, however, to judge from the published descriptions, that there is considerable variation in the symptoms of this disease in different places and in different epidemics. Thus, certain authors mention swelling of one or more joints as a common and prominent symptom, also metastasis of the pains, enlargement of the submaxillary glands, orchitis, and so forth, as being frequently present. These in my experience were very rare. However this may be, the essential features in well marked cases are practically very much alike everywhere and in all epidemics; nearly all writers accentuate, as leading

and characteristic symptoms, the suddenness of the rise of temperature, the initial stage of skin congestion, the pains, and the terminal eruption.

**Relapses** of dengue are not uncommon, and second and even third attacks during the same epidemic have been recorded. As a rule, the susceptibility to this disease is exhausted by one attack.

The incubation-period seems to be somewhat variable. It is certainly not a long one. I have seen a case in which it could not have exceeded twenty-four hours. Some observers place it at five or even seven days, but this is an over-estimate. One to three days seems to be near the truth.

**Epizootics concurrent with dengue epidemics** have been noted in Spain in 1784, and at Baroda and Rangoon in 1872. The animals affected are said to have shewn symptoms of paresis of one or more limbs.

**Diagnosis.**—The diseases most likely to be confounded with dengue are German measles, scarlatina, measles, syphilitic roseola, influenza, rheumatic and malarial fevers. A knowledge of the distinctive features of these various diseases, and of the fact that dengue is attended both with a rash and with articular pains, and that it occurs in great and rapidly developed epidemics, should prevent any serious error in diagnosis.

**Mortality and Prognosis.**—In uncomplicated dengue the direct mortality may be said to be almost nil. In the case of very young children convulsions or delirium may occur and cause some anxiety; and in the aged and infirm, and in those suffering from chronic exhausting disease, an attack of dengue may prove a serious complication. Charles describes a pernicious form which, though rare, was very much dreaded in Calcutta; in these cases the lungs were oedematous, and the patient, becoming drowsy and cyanotic, quickly passed into a condition approaching hyperpyrexia and died. Some writers state that the gravity of any given case is in direct proportion to the abundance of eruption; others deny this. In the European in hot and unhealthy climates an attack of dengue very often leads to a condition of debility necessitating temporary change of climate, or even a return to Europe. In both Europeans and natives the attendant lowering of the resistive powers disposes to other and more dangerous diseases, such as malaria, yellow fever, dysentery, pulmonary tuberculosis, and so forth. Consequently dengue, otherwise a benign disease, may become a source of public danger. It is probable that it is in this indirect way that the general mortality rises during the epidemic visitation of this disease.

**Nature of Dengue.**—There can be little doubt that dengue belongs to the same class of diseases as measles, scarlatina, and the other exanthematous fevers. Analogy distinctly points to this. Certain writers, however, oppose this view; principally on the ground that the epidemic extension of dengue is so rapid and so wide that there can be no time for the operation of infection from person to person. Such writers invoke some vague telluric or atmospheric influence to explain the rapid extension of the disease in epidemics, and the tendency it exhibits from

time to time to become rapidly pandemic. But if we bear in mind the shortness of the incubation period, the almost universal susceptibility of the population unprotected by a recent visitation of the disease, the frequency of mild attacks, which, even during their height, do not incapacitate the subject of them from walking about the streets and thus diffusing the infection far and wide, and the marked tendency it shows to prevail especially in towns and densely populated quarters, one can readily understand that the entire population of a city may be exposed to and acquire the disease within a fortnight of the importation of the first case. Dengue in this respect closely resembles influenza. A highly infectious, but not in all cases nor generally a very disabling disease, to which nearly every one is susceptible, and which has a short incubation-period, is bound to spread rapidly when introduced into thickly populated districts.

As to the nature of the poison or germ of dengue there are no well-established data on which to base a very definite opinion. Bacteria, of course, have been described in connexion with this as with every other fever, but the value of the observations is at best doubtful. Probably the germ of dengue resembles those of the other exanthematous fevers, which, with the exception of that of enteric fever, are still hypothetical. It is a singular and suggestive circumstance that, although some of these exanthematous fevers prevail and spread during the cold season in the tropics as readily as during the hot, there are others—yellow fever and dengue—which cease at once to extend when the temperature of the atmosphere sinks below a certain point. Conversely there is one fever, common enough in cold and temperate climates, which seems to be killed down by the high temperature of the tropics, namely, scarlet fever. As the temperature of the human body is fairly uniform in all climates, any restraining influence which high or low temperature may exert on these disease germs can only operate when the said germs are outside the body, and as they pass from one person to another. The fact that these germs are so easily killed, or rendered inert, by insignificant differences of atmospheric temperature during what must be but a momentary exposure seems to tell very strongly against the supposition that these organisms are bacteria; for such bacteria as we know are organisms which, for the most part, possess great powers of resistance both to high and low temperatures, and are certainly in all cases well able to withstand such inconsiderable elevations and depressions of temperature as occur naturally either in the temperate or in the tropical zones. Analogous and similarly suggestive contrasts in their heat resisting capacities are supplied by the malaria germ, and by the hypothetical germs of beriberi and rheumatism.

Graham describes an endocorpuseular organism resembling *Haesna biguttata* which he says he found in dengue blood in a recent Syrian epidemic. He further mentions several experiments which led him to conclude that the infection was transmitted by the common mosquito *Culex fatigans*. Other observers have entirely failed to confirm Graham's statements, but Bancroft in Australia regards the virus of dengue as



analogous to that of yellow fever both in respect to its ultra-microscopic minuteness and its transmission by *Stegomyia fasciata*. His experiments as regards the rôle of the latter are few and contradictory; nevertheless the epidemiology of the disease is quite in keeping with such a hypothesis.

**Treatment.**—Were it possible to secure perfect isolation for an individual during an epidemic of dengue there can be little doubt that he would escape the disease. Even comparative isolation is attended with diminished liability. In Amoy, in the epidemic of 1872, those foreigners who lived in a more or less rural and isolated situation were very much less affected than were those who lived in the Chinese town, or than those whose occupations threw them much in contact with the natives. This and similar facts point to the theoretical possibility of thus avoiding dengue during an epidemic; but in the ordinary circumstances of life in the tropics such precautions would be impracticable.

Like the allied fevers dengue runs a definite course; it is useless to attempt to abort or cut it short. The patient should go to bed as soon as he feels ill, and he should keep his room until the terminal eruption has quite disappeared and he feels well again. Ten days is not too long to allow in severe attacks. As in influenza, rest, light diet, and the avoidance of chills conduce powerfully to a speedy and sound convalescence. At the outset of the fever some saline diaphoretic mixture with aconite may be prescribed, perhaps with advantage. If the pains be severe and the fever high, antipyrin, or antifebrin, or belladonna will give great relief. Cold applications to the head are comforting. If the temperature rise to 105° F. or over, cold sponging or the cold bath ought to be used. If the pains continue to be very distressing, a hypodermic injection of morphine will afford welcome relief and do no harm. Purgatives and emetics should be avoided, unless pronounced constipation or a history of a recent full meal urgently demand their use; the pain caused by the disturbance of the patient more than counterbalances any advantage they might otherwise bring. The diet during the fever must be liquid; afterwards light and nutritious. Wine in the early stages is not advisable. Freshly made lemonade and iced water will be found to be the most acceptable drinks during the fever.

For the pains experienced during convalescence, rubbing with an opium or belladonna liniment, gentle massage, electricity, salicylates, small doses of iodide of potassium, and quinine have each been advocated. Debility and anorexia indicate tonics such as quinine, strychnine, mineral acids, vegetable bitters, and change of air.

PATRICK MANSON.

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P. M.

JAPANESE RIVER OR FLOOD FEVER<sup>1</sup>

By F. M. SANDWICH, M.D., F.R.C.P.

SYNONYMS.—The Japanese call this disease *yōchūbio*, *shima mushi* (island-insect), *aka mushi* (red insect), *kedani* (hair-louse), or *Tsutsugamushi*. Fr. *Fièvre fluviale du Japon*.

DISTRIBUTION.—This fever, first described by Palm, Bälz, and Kawanishi, has so far not been recognised in other countries, and even in Japan it is limited to the banks of rivers on the west coast of the largest island. These rivers are the Omonogawa and Minasegawa in the Akita district, and the Shinanogawa, Akagawa, Uwonumagawa, and the Sadegawa in the Niigata district. The disease is said not to occur along the whole length of these river banks, which are flooded every spring and summer, but to be restricted to certain localities; and it has been reported from the banks of other Japanese rivers which also flow regularly.

CAUSES.—River fever, though infectious, is not contagious, for there is no record of transmission directly from one individual to another. As bacteriology and the insect or other means by which the virus is conveyed are unknown, our knowledge is confined to the factors associated with the disease. According to Bälz, it is limited to the flooded valleys already mentioned; the river banks, when the flood subsides, are sown with hemp and corn, and during the harvest in July and August the disease appears. It is chiefly confined to the harvesters, but occasionally arises among other men who are working near the river, even though they have apparently not come into direct contact with the flooded soil, nor with the harvested hemp or corn. We must, therefore, assume that the virus can, in favourable circumstances, be conveyed a short distance by means of soil, clothes, corn or hemp, or that transmission takes place in consequence of the bite of an insect, which may or may not be the carrier of the virus. We may reasonably assume that the poison enters the body at the spot where the local scab and painful lymphatic glands are discovered. Bälz disbelieves the assertion of Japanese physicians that the illness is conveyed by an insect which bores into the skin, like the harvest bug (*Leptus autumnalis*) of Europe.

Tanaka, in three patients, found a species of proteus, with staphylococci and streptococci in the sputum and urinary sediment, and at the autopsy was able to confirm its presence in the lungs. He therefore considers that this micro-organism is the cause of the disease.<sup>2</sup>

The writer pretends to no personal knowledge of this disease, but has been invited by the Editors to compile a short account of it from the sources available.

In a paper which appeared while this article was in the press, Ogata (4A) states that the disease is due to an amœboid protozoon (sporozoon), which he calls Kedanisporozoon, reared by young lice living on plants. He found the sporozoon in the blood and organs, reared a pure culture, and reproduced the disease in animals.



*Ser.*—All ages and both sexes are considered liable, though men, being more exposed to the infection than women and children, form the bulk of the patients. Pregnant women, if attacked, often miscarry and die.

**Morbid Anatomy.**—Very little seems to be known about the pathological results of this disease, but it is interesting to note that no local lesions of importance have been discovered. In two autopsies Kawakami noted hypostatic congestion of lungs, inflammation of the bronchi, a soft and friable condition of the myocardium, enlargement of the spleen, and slight perisplenitis. The small intestine near the ileo-cæcal valve was injected in patches and shewed somewhat raised areas, not always corresponding to Peyer's patches; the mesenteric glands were a little swollen, and the peritoneum was injected. Both the patients had, however, been drunkards.

The incubation varies from four to seven days. One attack does not confer immunity, for several attacks have been observed in the same person.

**Symptoms.**—The fever has a fairly sudden onset, and is ushered in with rigors, headache, chiefly in the temples and forehead, anorexia, general malaise, and debility. On the first or second day the patient complains of pain in the lymphatic glands of the inguinal, cervical, or axillary region; and on examination a small, round, dry, blackish scab can be found near the genitals, or on the skin of the hypochondria, neck, or armpit. This scab, which appears to be present in every case, is from 2 to 4 mm. in diameter, hard to the touch, and at first tightly adherent. The skin around the scab is soft and dull red in colour, but not painful or tender, though there is sometimes a little tenderness on pressure along the lymphatics leading from the scab to the neighbouring glands. The glands affected are enlarged, freely movable, and tender on pressure, and do not suppurate. The inflammation is not confined to the glands nearest the scab, but in a milder degree affects other superficial glands.

The temperature during the first few days varies between  $101^{\circ}$  and  $103^{\circ}$  F., conjunctivitis is generally present, and there is a slight dry cough. The tongue is moist and slightly coated, marked constipation is present, the urine is scanty and often contains albumin (Tanaka). The spleen is always slightly enlarged. On the sixth or seventh day when the fever, which is continued in character, has reached  $104^{\circ}$  or more, an eruption appears, first on the face, spreading to the trunk, legs, and forearms, though it is said to be less marked on the thighs and upper arms. The eruption consists of large, irregular, dark-red papules, which become confluent on the cheeks; occasionally a few punctiform spots are seen on the palate. The eruption indicates the height of the disease, and, in a characteristic case, may last from four to seven days, though in mild cases it may be present for one day only. The pulse is seldom very quick. The patient can answer questions, but there is often slight deafness and delirium at night. He complains a good deal of tenderness in the skin and muscles, the lips are dry and cracked and bleed easily, while the tongue is dry, coated at the tip and edges, and denuded of epithelium in the centre. In severe cases the epigastrium and left

ochondrium are tender on pressure. During the second week the b falls off and leaves in its place a punched-out ulcer, discharging a le pus. About the end of the second week, in an ordinary case, the ient perspires freely, and the temperature slowly returns to normal, ile there is a general improvement in all the other symptoms. The etite returns, slight diarrhoea occurs, the urine becomes more copious, l convalescence is now rapid; but the ulcer may take some weeks to l entirely, and the glands in its immediate neighbourhood may tinue to be painful.

In mild cases there may be no recognised constitutional symptoms; fever is so trifling that the patient never keeps his bed, the eruption bsent or unnoticed, but the circumscribed necrosis of the skin and the ndular inflammation are always present. Such benign cases last only a ek, but the average duration of a moderately severe attack is three weeks.

**Complications.**—The patient's life is endangered by the complications ich may accompany or succeed a very serious attack, such as parotitis, læna, coma, mania, cardiac weakness, and œdema of lungs. Bälz imates the mortality at 15 per cent, while Tanaka considers it may etimes be as high as 70 per cent.

The treatment must of course be symptomatic. Scheube, after many ars' experience in Japan, points out that the Japanese react to anti-retics much more easily than Europeans.

F. M. SANDWITH.

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F. M. S.

## PLAGUE

By J. F. PAYNE, M.D., F.R.C.P.

### Bacteriology and Specific Treatment

By W. BULLOCH, M.D., and Capt. S. R. DOUGLAS, I.M.S.

**SYNONYMS.**—*Oriental plague, Bubonic plague, Pestis, Pestilentia: Pali plague* or *Mahamurrie* (in India). The *Black Death* (fourteenth century in Europe).

**Definition.**—An acute infective febrile disease, accompanied by inflammation of lymphatic glands, caused by a micro-organism, the *Bacillus pestis*.

**History of the Plague.**—The first historical notice of a disease like bubonic plague records its occurrence in Libya in the third century before Christ, or earlier: but this notice is only contained in a fragment from the writings of a much later physician, Rufus of Ephesus (about 100 A.D.), who also speaks of its occurrence in his own time in Libya, Egypt, and Syria. Whether it was clearly known to the classical Greek writers on medicine is doubtful, but Aretæus speaks of *βουβῶνες λοιμώδεις* or pestilential buboes. The plague of Athens described by Thucydides was apparently not this disease; nor was the destructive pestilence in the reign of Marcus Aurelius alluded to by Galen. We meet with bubonic plague again, however, in the great Plague of Justinian, which started from Egypt, 542 A.D., and spread over a large part of Europe; it was described in Gaul as *lues inguinarum*. Epidemics succeeded one another in this and the succeeding century. At the end of the seventh century bubonic plague prevailed in Italy and is unmistakably recorded by Bede in England. But after that time it is difficult to follow the track of plague. Many European pestilences are spoken of in mediæval histories, which may or may not have been bubonic plague, though no sufficiently clear record remains.

In the fourteenth century a new era began. All previous European plagues could be traced back, directly or remotely, to Africa, and for the most part to Egypt; but now a new epidemic invaded Europe from Asia by way of the Crimea and the Black Sea, its origin being referred to Cathay or China. This terrible pestilence, afterwards known as the "Death," or the "Black Death," appeared in Southern Italy in 1346-47, and made its way over the whole of Europe. It reached England early in 1348, and for several, probably five or six, years was prevalent in various parts of the country. Scotland and Ireland were affected in their turn; and no country in Europe seems to have escaped. A second epidemic occurred in 1361, and a third in 1368. The details of this great calamity have often been dwelt upon by historians, and cannot be

seen here. It is calculated by Hecker that 25,000,000 persons, one-ninth of the population of Europe, died of this disease. Although it has been doubted whether this was the true bubonic plague, it must now be accepted that the Black Death was that disease in a peculiarly virulent form. The first epidemic was evidently one of what is now called pneumonic plague.

The great importance of this event in epidemic history is that from that time forth, whether previously or not, plague was established as an endemic disease in England and other parts of Europe; though it is quite possible that, as Hirsch and others think, fresh importations of the virus from the East took place from time to time. The successive epidemics in Britain through the fifteenth, sixteenth, and seventeenth centuries are well recorded in Dr. Creighton's *History of Epidemics in Britain*. Finally it culminated in that called the Great Plague of London in 1665, in which about 70,000 persons died, and which extended widely over the country. Soon after that the disease vanished, never to recur on British soil till a localised epidemic occurred in 1900 at Glasgow.

During these centuries most countries in Europe suffered from repeated epidemics. It was noticed that the epidemic wave passed on the whole from East to West, or from the Mediterranean countries northward; this led to the belief that many European epidemics were derived from more persistent foci of plague in Turkey, the Levant, and Egypt. Hence the system of quarantine, by sea and land, was introduced to stem the tide of infection. This belief, which is that of many epidemiologists, receives support from the fact that the disease died out earlier in Western than in Eastern Europe. Holland, France, Spain, and Italy became exempt, with one notable exception, a little later than England—about the end of the seventeenth century. Eastern Germany lingered somewhat longer, while in Poland, Russia, parts of the Austrian Empire, and the Danubian countries, epidemics were repeated throughout the eighteenth century. There was thus a general eastward recession; the chief exception to which was the great epidemic of Southern France, 1720-21. This was generally attributed to the arrival, in the port of Marseilles, of a ship from Syria infected with plague, which then spread to the populous and insalubrious city. The invasion of islands like Sicily and Malta in the eighteenth century was clearly due to the same cause, namely, to a contagion imported by sea.

During the first half of the nineteenth century plague prevailed in Turkey, and made occasional advances into the Danubian countries, to the shores of the Adriatic Sea, and to the south of Russia. Being still most constantly present in Egypt and Syria, it seemed to be peculiarly a disease of the Eastern Mediterranean, and thus acquired the name of Oriental Plague, which has lasted to our day; and the strictest precautions were still taken in all the Mediterranean ports to prevent its invasion.

Finally in 1841 plague left Europe by its Eastern gate, Constantinople; and in 1843-45 it became extinct also in Syria and Egypt, so that

the old Levantine Plague seemed to have entirely vanished. It is clear, however, that in Asia Minor it did not die away, but only receded eastward. At the beginning of the nineteenth century, the Caucasus, according to Tholozan, was the centre from which epidemics radiated; but in the latter half of the century that centre was shifted to the mountains of Kurdistan.

Good authorities still held that the disease was probably not extinct; and these suspicions were confirmed by accounts received at Constantinople, in 1853, of an outbreak in the Azir district of Arabia: this outbreak has been followed by others at intervals of some years; the last was in 1889. In 1858 the same disease was heard of in Benghazi, where it must have prevailed at least two or three years before; and there it appeared again in 1874, and possibly again later. The plague has also recurred in the form of epidemics which were relics of the former wide distribution of plague along the whole northern coast of Africa, and in the province of Tripoli so lately as 1837.

The more recent accounts of plague in the Kurdistan district, on the frontiers of Turkey and Persia and Mesopotamia, begin with 1863; but this was not the first appearance of the disease in that part of the world—Baghdad and the neighbourhood had suffered severely at the beginning of that century, and, for all we know to the contrary, for centuries before that. The chief known recent epidemics of Persia and Kurdistan were in 1863, in 1870-72, and in 1876-77; in 1877 a terrible epidemic occurred also in the town of Resht on the Caspian, which is an important occurrence in relation to the epidemic of 1878 on the Volga. The latest recorded appearance of plague in Persia was in 1885; but it was probably not the last. In Mesopotamia (Irak-Arabi), from 1856 onward for several years there prevailed what is now known to have been the mild form of plague. In 1867 a definite epidemic was recorded; in 1873-74 another extending over a much wider area; and in 1876-77 one still more extensive, and very severe. A further outbreak occurred in 1880-81, which is said to have destroyed one-quarter or one-third of the population; and another in 1884.

The above short record is of interest as shewing how plague may extend its area in successive epidemics; and also as leading up to the comparatively small epidemic on the Volga in 1879, which caused so much alarm.

As has been shewn, in the years 1876 and 1877 the plague was very active. In June 1877, and also in the two years following, a febrile malady accompanied by buboes appeared in Astrakhan, on the northern shore of the Caspian, a place in direct communication with Resht on the Persian shore, and it extended to neighbouring villages. Though it was of a mild type and caused but few deaths, it was certainly the mild or minor form of plague. In October 1878 a similar but more severe epidemic broke out in the Cossack settlement of Vetlanka, 130 miles up the Volga; and by December it assumed the character of the most virulent plague. The epidemic lasted in this village till 24th

January 1879; but in December it had already spread to other villages, which nearly every patient died. The last death in the district occurred on 9th February. Though affecting a small population it was very fatal, causing 382 deaths in a population of 1700. The mortality was nearly 90 per cent of the cases.

This is the simple history of the epidemic which caused a panic throughout Europe. It is easily explained when we see its filiation with the mild epidemic of Astrakhan and the severe one of Resht; and the general prevalence of plague in Persia in previous years. A minor epidemic in 1877 at Baku, on the western shore of the Caspian, furnishes another link. Why the disease was so mild in Astrakhan and so virulent in Vetlanka we cannot tell; but a like sudden development of the severe out of the mild form of the disease is frequently observed.

*History of Plague in India.*—Plague has been little known in India since English settlement and occupation, and the climate has been thought to be too hot for it: a supposition signally falsified by recent events. Recent historical research has brought to light records of epidemics of plague in India from the eleventh to the end of the seventeenth century. In the seventeenth century it was particularly severe. In 1655 a great epidemic, which lasted for eight years, affected the Punjab, Oude, Agra, and Mahometan India generally. From 1684 to 1702 and 1707 an epidemic ravaged Bombay, Surat, and a great part of Western India. Plague then disappeared from India (as it did about the same time from Western Europe) for more than a century, but reappeared in the nineteenth century in three distinct centres. In 1815 an outbreak, following a famine, occurred in Cutch, Guzerat, and Hyderabad. The next year it reappeared, but went away in 1820. In 1816 an epidemic which broke out at Pali in Rajputana became known as the Pali plague, but it ceased in 1838. In a different locality, the districts of Gurwhal and Kumaon on the south-west of the Himalayas, a disease known locally as Mahamurrie (which is undoubtedly bubonic plague) has recurred several times since 1823. The last great epidemic was in 1876-77, but it recurred in 1886, 1888, 1893, and 1897. No connexion can be traced between the above-mentioned localities of plague, nor between them and any other. The outbreak of plague in Bombay in 1896 is best considered in connexion with plague in Persia.

*History of Plague in China.*—The first definitely known epidemic of plague in Yunnan was about 1860; but it is believed to have existed there at least since 1850, and probably long before. There was an epidemic at the beginning of the nineteenth century. It is said to have recurred nearly every year up to 1893. In Pakhoi it is also frequent, but was absent from 1884 to 1893. The epidemics of Pakhoi were derived, it is probable, from Yunnan, and it is impossible to trace the derivation of the disease from any other district. From Pakhoi it must in some way have found its way to Canton, where it broke out in January 1894.

Rennie of Canton thinks it passed by land, since in 1891 a severe



epidemic occurred in the district of Kaochoo, lying to the north of Pakhoi; and in the spring of 1894 it prevailed in towns to the south of Canton. From Canton to Hong Kong it was carried by the busy and continual traffic between the two places. It spread also to Macao, and other places on the coast, but not, it would seem, far inland in China. The mortality of Canton in 1894 is variously given from 40,000 to 100,000.

*The Modern Period of Plague.*—The extension of plague to the great seaport of Hong Kong has proved to be one of the most momentous events in the history of the disease. The first epidemic in Hong Kong lasted from May to August 1894, and caused a mortality of 3000. It has recurred, with a varying mortality, every year since, except 1895. The social conditions, filthy habits, with excessive overcrowding in small, dark, unventilated rooms generally situated over great warehouses swarming with rats, supplied a very favourable soil for the disease. But the most important point is that the communication of the port (as also that of Canton) by sea traffic with almost all parts of the world has carried plague to seaports in India, Australia, Japan, Europe, Africa, and America, North and South. This general distribution has completely changed the aspect of a map shewing the parts of the world affected with plague, which has now become a "pandemic" and not merely a local epidemic disease. But its filiation is clearly traceable to the endemic centre of Yunnan in China.<sup>1</sup>

It was in Hong Kong that the *Bacillus pestis* was discovered by Kitasato, and later, but independently, by Yersin (*vide* p. 365). Passing over the nearer epidemic foci which were set up, we come to Bombay, where plague appeared early in 1896. Bombay, which had been free from plague for nearly 200 years, has an active trade with Hong Kong, and as the disease first appeared near the docks where the Chinese trade enters, and no other source of infection could be traced, it is almost certain that the infection came from China. The precise date and manner of conveyance of infection could not be traced, since the disease was, as usual, first overlooked; but before the outbreak among men was perceived, rats are known to have been dying in large numbers, so that it is most probable that rats conveyed in ships were the channel of infection. The disease was at first mild, and, as is usual in such cases, the diagnosis of plague was received with doubt or denial till, in October 1896, Haffkine's bacteriological investigations left no doubt on the matter. The disease spread from the dock-quarter to other parts of the city. Active preventive measures were taken, but were hindered by the active resistance of the population. In February 1897 the highest mortality was reached. Nearly half the population left the city in a panic, carrying the infection to other parts, and, since then, plague has never been absent from Bombay.

<sup>1</sup> A map of the present distribution of plague is given in Dr. Simpson's "Treatise on Plague." Comparative maps shewing the distribution before and after 1894 were given in the *Quarterly Review*, Oct. 1901.



The terrible increase of plague throughout India may be seen in the following table of official statistics, which are probably less than the actual mortality :—

DEATHS FROM PLAGUE IN INDIA

1896-97 (Bombay Presidency only)	. .	57,965
1898 (chiefly Bombay Presidency)	. .	118,103
1899	. . . . .	134,102
1900	. . . . .	91,627
1901	. . . . .	282,496
1902	. . . . .	574,493
1903	. . . . .	853,573
1904	. . . . .	1,040,000
1905	. . . . .	945,405 <sup>1</sup>
Total for ten years		4,097,764
Average annual mortality		409,776

In the earlier years Bombay Presidency shewed the highest mortality, but in 1904 the Punjab took the lead with the enormous mortality of 350,000 in a population of less than twenty-seven millions.

The infection gradually spread to other places in the Bombay Presidency ; Poona, near at hand, and Karachi, on the Persian Gulf, were infected in the same year, and many less important places, so that by June 1897 the plague had obtained a wide diffusion. The details may be read in Dr. Simpson's excellent work, but must be passed over here. In 1898 and 1899 the epidemic assumed larger proportions and caused a much higher mortality. From the Bombay Presidency the epidemic gradually spread over a large part of India. In Calcutta there were in 1896 some imported cases, but no serious outbreak took place till 1898. Nevertheless, in 1899, the Royal Commission, on leaving India, spoke somewhat hopefully. Since that time, however, the epidemic has every year enlarged its boundaries, and increased in its fatality. The Central and North-West Provinces, several native states, and Bengal have been overrun. The plague has extended far into the Madras Presidency, though on the whole with a much lower mortality, and the city of Madras has, apart from some imported cases, remained free ; as has the southern part of the Presidency. In 1906 the mortality was much lower than in 1905. Thus, in the first six months of 1905 the deaths numbered 876,735 ; while in 1906 the recorded mortality for the corresponding period was only 234,356 ; and the whole mortality for 1906 will probably be not more than a quarter of what it was in the year before.

Leaving India we must briefly indicate the further distribution of plague over the world. In 1898, for the first time in its previously known history, plague reached the Southern Hemisphere at the port of Tamatave in Madagascar, possibly from Bombay or from Cutch or some

<sup>1</sup> Of which 876,735 occurred in the first six months of the year.

other port on the Persian Gulf. From Tamatave cases were carried to Lorenzo Marquez on the African coast, but no epidemic resulted, though in the next year plague prevailed in the adjacent parts of Mozambique. In 1898 or 1899 plague appeared at Port Louis in Mauritius, where it has continued ever since; it was thought to be derived from Tamatave. In 1899 Penang in the Straits of Malacca, and Manila in the Philippines, were affected. In the Pacific, Numea in New Caledonia, and Honolulu in the Sandwich Islands, received the infection. In Australia, Sydney had a definite though limited epidemic, clearly traced to rats in the port, but whether from Hong Kong or from Numea was uncertain. There was a limited epidemic in Queensland, while Melbourne, Adelaide, Perth, and Auckland received some imported cases, but the epidemic was arrested. Western Europe, after nearly two centuries of exemption, witnessed a serious epidemic of plague at Oporto in 1899, or perhaps originating earlier. The source whence it was infected was not clear, but probably it came from India. Lisbon suffered later, but less severely. So strange are the ways of plague, that from Oporto the Western Hemisphere for the first time in history became infected. Plague was first recognised at Asuncion, an inland port on the river Plate, and it afterwards appeared at Santos in Brazil, Rosario on the river Plate, Buenos Ayres, and Rio de Janeiro. In the same year plague appeared in its old home, Egypt, at Alexandria, on the highway between India and Europe. It has more than once since reappeared in Egypt, but that it has not taken root in that classic land of plague must be set down to the excellent measures taken by the Egyptian medical authorities.

In North America, San Francisco has more than once been the scene of small epidemics of plague, confined to the Chinese quarter and apparently introduced from China. Some ports in Mexico are said to have been infected with plague, but the evidence was not quite complete. The disease has been carried to New York by shipping, but has not caused any epidemic.

In 1900 plague again crossed the Atlantic, this time from West to East, being brought by a ship from Rosario to Cape Town, where, in spite of quarantine precautions, it invaded the city and spread also to Port Elizabeth. Other outbreaks in South Africa were reported during the war and since, chiefly in the ports, but one outbreak occurred at Johannesburg. The plague, however, does not seem to have taken root seriously in that country.

Recently plague has spread to new regions. Towards the end of 1905 it broke out in Seistan, a district in the east of Persia, bordering on Afghanistan, quite remote from the older seats of plague in Western Persia, bordering on Kurdistan. It seems probable that this epidemic was derived indirectly from India, but the connexion cannot be precisely traced. A great mortality among rats was observed.

A fresh recurrence has been observed during the winter 1905-6 in the Russian province of Astrakhan, on the banks of the Volga, at Krasnoi Jar, close to Vetlanka, the scene of the fatal outbreak of 1879.

The mortality was not large, but the rate of case-fatality was 95 per cent. No mortality among rats has been recorded. Recent outbreaks in the neighbouring districts bordering on the Caspian make it probable, as some think, that there is an endemic centre of plague in those regions.

Plague has continued to prevail in its old seats, Hong Kong and Southern China, while epidemics are reported from Japan, Formosa, and Mauritius, but on the whole with diminished mortality. From the South American ports, as Rosario and Buenos Ayres, plague is still reported from time to time ; and on one occasion occurred on a steamer arriving from those parts at Hamburg, but did not spread to the port.

The small epidemic at Glasgow in 1900 was the first known in Britain since the great plague of London. It was strictly limited by preventive measures, but affected about thirty persons, of whom eight died. Contrary to the experience of almost all recent epidemics in sea-ports, no mortality among rats was observed, and the source of infection was not traced (*vide* p. 378). Since the general diffusion of plague by sea traffic, cases have been imported to several British ports—Liverpool, King's Lynn, Cardiff, Bristol—and a few have been brought to London, but it has always been found possible to prevent an epidemic. In May 1906 a few cases occurred at Leith, possibly due to infected rats.

In Australian and South African ports plague-infected rats have been on several occasions detected, but no human epidemic has resulted.

On the whole, plague has shewn in all parts of the world diminished virulence and less tendency to spread.

J. F. P.

**Bacteriology.**—The cause of plague is the *Bacillus pestis*. During the Hong Kong outbreak in 1894 the Japanese Government sent Kitasato and Aoyama to investigate the disease. Arriving at Hong Kong on 12th June, Aoyama made an autopsy on 14th June, and Kitasato found numerous bacilli in the buboes, heart-blood, liver, and spleen. Similar bacilli were also found in a living case of plague on the same day. On 15th June cultures had developed, and with the exception of pigeons, all the animals inoculated by Kitasato died with signs identical with those of human bubonic plague. Yersin, sent by the French Government, arrived in Hong Kong on 15th June, and independently discovered the same bacillus, which has since been called *Bacillus pestis*. In the twelve years which have elapsed since the discovery of Kitasato and Yersin an immense literature on the plague bacillus has accumulated, and it has been identified all over the world as the cause of plague. In the great Indian outbreak it was studied by Hankin, Childe, Haffkine, and others; and as the epidemic increased in magnitude Commissions sent by various European Governments proceeded to India, working especially in Bombay. The results of their investigations have been published in a series of reports, of which the most important are the splendid work of Albrecht, Ghon, and Müller of the Austrian Commission (3), the report of the German Commission (19) (Gaffky,

Pfeiffer, Sticker, and Dieudonné), the exhaustive analysis of the Indian Plague Commission (Fraser, Wright, and Ruffer), and the Reports on Plague Investigations in India issued by the Advisory Committee appointed by the Secretary of State for India (1906) [77A]. The Russian Commissioners (Wyssokowitch and Zabolotny) also contributed many valuable additions to our knowledge. Apart from India and Hong Kong, the bacillus was studied in Formosa (Ogata (73) and Yamagiwa), Alexandria (Gotschlich (31)), Japan (Kitasato and Shiga), Sydney (Thompson and Tidswell), Oporto (Kossel (56), Calmette (9), Vagedes), and in South America (Voges and Uriarte).

A number of laboratory studies have also been completed in Europe, mostly in special plague laboratories by Nuttall, Kolle, Otto, Martini, and Kossel in Berlin; by Markl in Vienna; by Roux and Metchnikoff in Paris; Lustig and Galeotti in Florence; Abel and Nocht in Hamburg, and by Klein, Hewlett, and Douglas in London.

Protection of human beings has also been carried out on a large scale in India, chiefly through the efforts of Haffkine with his plague vaccin.

At the present time we possess a fairly complete knowledge of the pure bacteriology of the plague bacillus. A great deal, however, still requires to be done, especially concerning the manner in which the bacillus is transmitted, and concerning the best means for producing a specific prophylaxis and cure.

Plague belongs to the group of Pasteurelloses (Lignières) or hæmorrhagic septicæmias (Hueppe), diseases due to microbes which are highly pathogenetic to vertebrates. In all cases these microbes invade the blood-stream acutely, and are found in large numbers over the whole body.

*Morphology of the Plague Bacillus.*—The plague bacillus as seen in plague lesions (bubo, blood) shews a considerable polymorphism. In general, three forms may be readily recognised, viz., short oval rods, long rods, and large oval, pear-shaped or round pale-stained involution-forms. Of these the predominating form is the short oval rod measuring  $1.5$  to  $1.7 \mu \times .5$  to  $.7 \mu$  (Albrecht and Ghon). The involution-forms occur most frequently in artificial media and in cadavers which have been maintained at relatively high temperatures ( $30^{\circ}$  C.). The onset of involution in cadavers has been studied by Sata, who finds that from the second day after death the bacilli begin to alter, especially in the liver and spleen. The alteration proceeds up to the fourth day, but after this time the plague bacillus could not be identified with certainty, as it was overgrown by other microbes. The tendency to the formation of involution-forms is important from a diagnostic point. In pure cultures all the forms of plague bacilli mentioned above are also met with. The occurrence of club-like swellings and branches on plague bacilli has been described by Albrecht and Ghon, Kolle (52), and Skschivan (87).

*Staining.*—The plague bacillus exhibits in a high degree the phenomenon of polar staining, the micro-organism appearing stained at the ends, but not at all or only slightly so in the middle. This can be well seen in

films stained by Romanowsky's method, or by first treating the film with dilute acetic acid followed by dilute carbol-fuchsin. Kossel and Overbeck recommend fixing the films in absolute alcohol which is then evaporated off. Although a striking feature of the plague bacillus, polar staining is by no means peculiar to it, as other Pasteurellæ closely allied to the plague bacillus may shew the same phenomenon. It is often difficult to stain the plague bacillus well in sections. Sublimate or alcohol are the best fixatives for plague tissues, the most suitable stains being carbol-thionin, or polychrome methylene blue with glycerin-ether treatment. The Unna-Pappenheim methylgreen-pyronin mixture gives very instructive pictures, the bacilli standing out of a brilliant pink colour. Although Kitasato described the plague bacillus as retaining to a certain extent the stain in Gram's process, other observers have all found it to be Gram negative. Contrary to the opinion of Kitasato and Gordon the plague bacillus is non-motile. Endospores have not been observed, and from the experiments made on the resistance of the bacillus to injurious influences, it is improbable that they are formed. In their earliest descriptions both Kitasato and Yersin described the occurrence of a capsule surrounding the plague bacillus. It can easily be seen in cultures and even in bubonic pus by Romanowsky's method or any of its modifications.

*Cultures.*—Growths of plague bacilli can be obtained between wide ranges of temperatures, viz. 4° to 43° C. Unlike most pathogenetic bacteria the optimum temperature for growth is about 30° C., a higher temperature being very apt to produce attenuation in the virulence. Although it can grow to a certain extent under anaerobic conditions, aerobic are much more favourable. On the surface of an agar plate at 30° C. colonies of plague bacilli are visible under a low magnification as small drops, like dew, at the end of twenty-four hours. In forty-eight hours they have a whitish-grey colour with transmitted light. The centre is usually granular, and in characteristic colonies there is a broad irregular or crenated edge. It has been repeatedly noted that atypical colonies of a yellowish-grey colour and with a regular edge make their appearance. The times at which the colonies appear on the plate are also different, some being delayed as late as forty-eight hours. Streaked on agar a fine greyish-white mass of somewhat slimy consistence develops in twenty-four to forty-eight hours.

*Salt Agar.*—On adding 2·5 to 3·5 per cent of sodium chloride to ordinary agar, Hankin and Leumann found that there was a very rapid development of involution-forms, the staining properties of which are usually very poor. The value of these forms, from a diagnostic standpoint, is considerable, as they occur quicker and with greater certainty in the case of *Bacillus pestis* than in the case of other bacteria which may otherwise closely resemble the plague bacillus. (Skschivan (87), Rosenfeld, Matzuschita.)

On the surface of *gelatin* plates, cultivated at 20° to 25° C., colonies of *Bacillus pestis* become visible to the naked eye in two to three days. At first transparent, they soon become greyish with a raised granular centre

and a filmy crenated flat margin. The structure of such colonies can be very clearly made out in contact preparations. As in the case of agar, the individual colonies differ from each other in their rate of growth, and also to a certain extent in appearance. Thus, Dr. Klein (48) has described atypical colonies which were not unlike growths of *B. coli*, and were composed of the short oval rod form of the bacillus, whereas in the "typical" colonies the bacilli are usually larger. In a gelatin stab-culture a thread-like growth appears in the track of the needle with a surface growth similar to that seen on a gelatin plate. The gelatin is never liquefied.

The growth on peptone *bouillon* has been described as characteristic. At first, a general cloudiness makes its appearance, then a deposit. Round the edge of the vessel a whitish ring of growth ensues, and this finally spreads over the surface as a fine membrane. As Haffkine shewed, a layer of oil or ghee favours the surface growth, the bacilli hanging down from the oil-drops in the form of stalactites. This stalactite formation is not, however, peculiar to *Bacillus pestis*. In old *bouillon* cultures the medium appears clear above and shews a granular deposit below. After three to four days the growth in *bouillon* often seems to stop, to reappear again and to go on for weeks. Indol is not produced.

In general the cultural diagnosis of the plague bacillus rests on the appearance of the surface colonies on gelatin at 20° to 25° C., and on agar at 30° C., the former being especially useful when the plague material is contaminated with other bacteria as occurs in *fæces*, sputum, etc.

*Vitality of the Plague Bacillus outside the Body.*—A very large number of experiments have been made to determine the degree of resistance which the plague bacillus manifests outside the living body. In general the resistance is slight. Pure cultures kept in the dark and prevented from drying can live for months or even years (N. K. Schultz (84)); a great deal depends, however, on the temperature at which the experiments have been carried out. Thus when kept at 37° C., Gladin found cultures alive up to two to three months, whereas at 15° C. living bacilli were still found for 260 days. Difference of opinion prevails as to how long the bacillus can exist in the presence of other bacteria. The German Plague Commission saw plague bacilli growing freely in cultures along with *B. coli*, whereas the Indian Plague Commission found in such experiments that the plague bacillus quickly died out. The German Plague Commission recovered living plague bacilli from a spleen which had been putrid for four days. From the putrid cadavers of plague rats, Otto (76) was able to demonstrate the plague bacillus (by inoculating guinea-pigs) up to sixty-one days, provided that the cadavers had been kept at a low temperature (6° C.). In bubonic pus Albrecht and Ghon found that the bacillus could survive for twenty days. With sterilised *fæces* inoculated with plague bacilli, growths were obtained up to the fourth day (German Plague Commission). In fresh water the bacillus has been found to exist as long as twenty days (Wilm, Abel (1)). Wurtz and



surges recovered plague bacilli in a virulent condition from sea-water after forty-seven days.

In previously sterile earth, in which the organic matter had been destroyed by heat, Gladin found the bacillus for two weeks, whereas if the organic matter were present it could live for three months. Even in non-sterilised earth Gladin was occasionally successful in getting cultures as late as two months. Marsh found that the plague bacillus could live for months in sterile cow-dung. The Advisory Committee on Plague in India (1906) made a number of experiments on the infectivity of floors grossly contaminated with cultures of *B. pestis*. Throughout India there are two common forms of floors, the one consisting of ordinary cow-dung mastered, when moist, on the top of beaten earth, the other consisting of a mixture of lime and sand, and commonly called "chunam." On cow-dung floors it was found that plague bacilli remain infective for forty-eight hours, as tested by inoculating scrapings into rodents. If the latter are permitted to run free on such floors infection was not observed later than twenty-four hours. In the case of grossly infected floors of "chunam" the destruction of the plague bacillus took place within twenty-four hours.

In buried bodies plague bacilli have been recovered at periods varying from three (Gotschlich) to thirty (Yokote) days. Sata and Klein (47A) were able to recover the bacilli from the bodies of guinea-pigs that had been buried for sixteen and seventeen days respectively. Zlatagoroff (113) found, however, that if cadavers were kept at 0° C., living plague bacilli could be grown even after 109 days.

*Resistance to Drying.*—Bubonic pus dried on a cover-glass at 28° to 30° C. was sterile after four days (Kitasato). In numerous experiments carried out by the German Plague Commission, plague material being dried on wool, silk, linen, glass, wood, etc., the latest period at which the plague bacillus was found alive was six days. Drying in an exsiccator over sulphuric acid at 29° to 31° C. is rapidly fatal to plague bacilli (Wilm, Abel (1), de Giaksa and Gosio, Gladin), but much depends on the temperature at which the experiments are carried out. In dust the bacillus appears to die out rapidly, Germanno finding that bacilli dried to a fine dust had been killed. This suggests that transference of plague by currents of air, except at very short ranges, is improbable. In grain and meal the plague bacillus died out within thirteen days (Hankin).

Exposure to light causes rapid sterilisation of plague cultures or other infected material. From bubonic pus dried on cover-glasses and exposed to light, Kitasato was unable to obtain living cultures after three to four hours.

*Heat.*—Dry heat at 100° C. kills plague bacilli in one hour (Abel (1)), at 140° C. in three minutes, and at 160° C. in one minute (Gladin). Experiments which have been made on the action of moist heat have yielded somewhat divergent results, no doubt because the individual bacilli possess varying degrees of resistance. At temperatures of 55° to 70° C. the German Plague Commission obtained sterilisation of cultures in ten minutes.



Albrecht and Ghon and Gotschlich found that even after being heated to  $55^{\circ}$ - $60^{\circ}$  C. for one hour cultures might still be infective for animals, although the media inoculated from such cultures remained sterile. Gotschlich heated agar emulsions to  $68^{\circ}$  C. for twenty minutes, and then kept them at  $65^{\circ}$  C. for sixty minutes, and found that although they were apparently sterile they were still infective. Kolle, however, maintains that if the culture mass be frequently shaken during the process of heating, a temperature of  $65^{\circ}$  C. renders it both sterile and non-infective. Dr. Klein (47) also regards a temperature of  $65^{\circ}$  C. as effective.

Exposure to *cold* has very little effect on the plague bacillus, as it can survive at a temperature varying from  $0^{\circ}$  C. to  $-20^{\circ}$  C. for as long as forty days (Wladimiroff and Kressling). Kasansky even found it alive in 5½ months at a temperature of  $-31^{\circ}$  C.; Gladin froze and thawed cultures daily, and the bacillus was still alive after forty days of such treatment.

*Resistance to Chemical Disinfectants.*—Cultures of the plague bacillus are easily destroyed by chemical antiseptics; thus, perchloride of mercury (1 per cent) destroys the vitality at once, 1 per cent carbolic acid or 1 per cent lysol in ten minutes, 1 per cent chloride of lime in five minutes, sulphuric acid 1 in 2000 also in a few minutes. No extensive series of experiments have been carried out on the chemical disinfection of plague bacilli under natural conditions in houses, soil, clothes, etc.

*Pathogenetic Action.*—The plague bacillus exerts a pathogenetic action on a large number of animals. Prominent among these in point of susceptibility are rats, guinea-pigs, mice, and monkeys, which succumb with septicæmia in a few days after the inoculation of very minute quantities of plague material. In other cases, as in the horse, dog, cat, sheep, cattle, goats, and pigs, inoculation is followed by a rise of temperature and the formation of a local lesion, ending mostly in recovery. Unless inoculated with enormous doses of highly virulent cultures, all birds shew a very high degree of immunity. In discussing the pathogenetic effects in animals, most stress must be laid on plague in rats, as there is a close connexion between plague in these rodents and outbreaks in man.

*Experimental Plague in Rats.*—All varieties of rats can be infected with the greatest ease through almost any channel. After subcutaneous inoculation of a minute quantity of a virulent plague culture the animals manifest definite symptoms of illness within thirty-six hours; the hair is ruffled, the breathing rapid, and a peculiar nervousness or apprehension is usually a striking symptom. The temperature is raised and the conjunctivæ suffused. At the site of the inoculation there is usually a definite swelling which increases up to the time of death, which in acute cases supervenes about the third day. The characteristic lesions seen after death are the enlargement of the regional lymph-glands which are deep red, while the surrounding connective tissue is œdematous and frequently hæmorrhagic. The spleen is much enlarged, dark and firm, and generally presents a peculiar dry surface on section. The lungs are more or less

congested and occasionally shew petechiae. Enlargement of the mesenteric glands is constant and the intestine is hyperæmic. In the blood-stained mucus found in its lumen plague bacilli can be demonstrated as in all other parts of the body. They are, however, in greatest numbers in the spleen and buboes. In some cases death may be delayed till the fifth to seventh day, in these cases necrosis of the buboes has set in. When the cultures are very toxigenetic the post-mortem appearances of plague may be masked and the bacilli not so uniformly distributed.

*Cutaneous Inoculation.* Peculiar interest attaches to the effect of applying plague cultures superficially to shaved areas of skin. The value of this method was first noted by Albrecht and Ghon in the case of guinea pigs. Kolle had only partial success, however, in the case of rats. In Captain Douglas's hands this was found to be a very effective method of producing a fatal pest septicæmia, for out of 167 experiments on rats only 3 per cent survived. Technically this method of inoculation is best carried out by placing the rat in a holder and shaving a strip in the middle line between the teats. A glass rod dipped in an emulsion of plague bacilli is then applied to the shaved area over an extent of one square centimetre. At the time of death, which usually occurs on the second to fourth day, the local lesion in the shaved area consists of three to six small vesicles with a slightly raised and inflamed base. The fluid of the vesicles contains an enormous number of plague bacilli and a few degenerated leucocytes. Where the skin has been less carefully shaved the whole area over which the culture was spread may be thickened, reddened, and rough, but without vesicular formation. Buboes are present in all cases, even when the animal succumbs as early as the second day. The buboes, mostly axillary in position, vary in size but are always teeming with plague bacilli. Suppuration of the buboes may occur in cases that recover or do not die till the seventh to tenth day. When a culture of plague bacilli has been applied to the skin of immunised rats the local lesion may be entirely absent; at other times a large ulcer involving the whole thickness of the skin results. Occasionally the local change is in the form of a carbuncle-like swelling in which the skin is undermined by pus which escapes through a number of openings. Intraperitoneal inoculation of very minute quantities of cultures produces a rapidly fatal septicæmia. In some cases death seems to take place mainly from intoxication, the bacilli being found chiefly in the peritoneum over the liver and spleen.

*Infection by the Mouth.*—When rats are fed on plague cultures or on plague cadavers, the bacilli become localised in the submaxillary lymphatic glands and give rise to buboes in this site. Later, the animals fall victims to a plague sepsis. Kolle saw submaxillary buboes in forty out of sixty rats infected *per os*. In four other cases the result was a primary pest pneumonia, and in two cases only the development of mesenteric buboes showed that the bacilli had passed through the intestinal wall. Captain Douglas was not so successful in experiments of this kind. Under natural conditions rats frequently infect themselves by gnawing the pest

cadavers of other rats, the bacilli gaining entrance through small abrasions in the nose and mouth and leading to buboes about the jaws.

In the intestine necrotic changes may be found in Peyer's patches. In half of Kolle's cases bacilli were also found in large numbers in the blood and organs. The faeces of rats infected by the mouth may contain virulent plague bacilli (German Plague Commission).

The German Commission were the first to shew that the inoculation of plague cultures on the unbroken nasal or conjunctival mucous membrane leads almost invariably to a fatal issue in about three days with cervical bubo and enlargement of the spleen. Batzaroff stated that a primary pest pneumonia frequently ensues after cultures have been inserted into the nose, but Bandi proved that in such cases the pneumonia is really secondary to the cervical bubo. The development of buboes in the neck after conjunctival inoculation is probably the result of the bacilli passing down the nasal duct into the lymphatic apparatus of the throat.

*Plague Pneumonia in Rats.*—Martini produced primary pest pneumonia in rats in thirty two out of thirty six experiments by causing them to inhale plague cultures atomised into a spray. The lesions in the lungs were sometimes lobular, sometimes lobar, pleurisy was frequent. Martini thought that the virulence of the cultures was exalted by passage from lung to lung, and that when these exalted bacilli were inoculated intraperitoneally or subcutaneously they had a great tendency to become localised in the lung.

*Chronic Rat Plague.*—Kolle and Martini have drawn attention to the occurrence of a chronic form of rat plague manifesting itself in encapsuled foci with caseous contents in the submaxillary and bronchial glands, and associated with induration of the lungs. Chronic rat plague has also been investigated by Captain Douglas, who found the bacilli localised in lesions of the lungs, spleen, and glands. In 104 partially immunised rats dying before the eleventh day after inoculation with virulent plague material, a lesion was found in the lungs and usually associated with pleurisy. In a few cases dying late (eighth to tenth day) or surviving after the eleventh day, Douglas found numerous sharply circumscribed small nodules of whitish colour in the spleen. The nodules, which often numbered several hundreds, were exactly like the lesions of chronic plague or pseudo-tuberculosis seen in guinea pigs. The spleen for the most part was much enlarged by the presence of the nodules, which contained large numbers of plague bacilli, especially in the centre. Chronic plague lesions were also met with in the liver and thymus glands, although the animals were apparently in good health. In chronic pulmonary or splenic plague emaciation is a common symptom. In two cases in which the bacilli, isolated from chronic lesions, were tested, they were found to be attenuated. In Kolle's experiments, however, it is to be noted that the bacilli were virulent.

*Experimental Plague in Guinea pigs.*—Like the rat, the guinea pig exhibits an extreme susceptibility to the plague bacillus, fatal infection

ensuing after cutaneous, subcutaneous, intraperitoneal, intranasal, and conjunctival inoculation, or from inhalation, or ingestion of plague cultures. The symptoms and signs of experimental plague in guinea-pigs are identical with those described in the case of the rat. Chronic plague in the guinea-pig, with the production of large granulomatous masses in the liver, peritoneum, and spleen, was first noted by Albrecht and Ghon.

Mice appear to be less susceptible to plague than either rats or guinea-pigs, although virulent cultures usually induce a fatal septicaemia in three to five days. Infection *per os* often yields negative results.

Unless virulent cultures are employed, rabbits often escape on account of a considerable degree of insusceptibility which they possess. Mungoses (*Herpestes*), squirrels (*Sciurus*) (German Plague Commission), bats (*Vesperugo* (Gosio)), jerboas, and sisels (Tartakowsky) are highly susceptible to plague. Skschivan inoculated a tarbagan (*Arctomys bobac*) subcutaneously, and produced a general pest sepsis with hæmorrhagic pneumonia, without local lesion or bubo. As was first shewn by Wyssokowitch and Zabolotny in Bombay, monkeys are highly susceptible to plague virus, a prick in the finger with a needle dipped in a culture leading to pest sepsis and death. Similar results were obtained by Albrecht and Ghon and by the German Commission. *Semnopithecus entellus* was found to be much more susceptible than the brown monkey of India (*Macacus radiatus*). Captain Douglas produced fatal sepsis in monkeys from conjunctival, nasal, and vaginal inoculation of minute quantities of plague cultures. Intratracheal inoculation gave rise to primary plague pneumonia. After ligation of the femoral or brachial veins, injection of plague cultures into the corresponding limbs caused typical buboes, sepsis, and death in a few days.

Dogs, jackals, and hyænas are mostly insusceptible, even after subcutaneous inoculation (Albrecht and Ghon). Plague bacilli may be passed *per rectum* after ingestion of plague-infected material. Ogata was able to infect cats, but the details of his experiments are not known. In the hands of the German Commission subcutaneous inoculation of cultures caused fever and local reaction, ending ultimately in recovery. Wilm, Kolle, and Hunter saw cervical buboes in cats fed on plague material. In four animals treated in this way Kolle had two positive results, one dying from pest sepsis with cervical bubo, the other recovering after a severe illness with great emaciation.

*Pigs.*—Wilm in Hong-Kong observed a rise of temperature and local oedema after subcutaneous inoculation in the flank. Dr. Lowson fed swine with large quantities of plague spleens, but they recovered. The German and Austrian Commissions, and also di Mattei, had similar negative results.

Horses usually react with local lesion and fever (Yersin, Calmette, and Borrel), and the same applies to cattle, sheep, and goats. Hedgehogs are immune (Nuttall), as are pigeons, fowls, ducks, singing-birds (Albrecht and Ghon, London), lizards, serpents, salamanders, and frogs (Nuttall). Devell states that he had positive results with *Rana temporaria*.

*Behaviour of Plague Bacilli in the Bodies of Insects.*—A very extensive

literature exists on the part played by insects in the dissemination of plague; the animals specially studied in this connexion being flies, bugs, mosquitoes, pediculi, ants, cockroaches, and fleas. Considerable differences might be expected according as the insects are suctorial or not, or according as those which infest animals such as rats are capable of transferring themselves to the body of man. In non-suctorial insects the plague bacillus may exist on the surface of the body, and may in this way be transferred to articles of diet, clothing, and so forth. Extreme interest also attaches to the question of the fate of the plague bacillus in the alimentary canal of the insects, and especially whether it is capable of multiplying in this site or undergoing changes in virulence either in the direction of exaltation or attenuation.

*Flies.*—In at least one instance Yersin found plague bacilli in the bodies of dead flies in the laboratory at Hong-Kong; Dr. Nuttall also succeeded in infecting *Musca domestica*, and he considered that flies might act as disseminators of the disease. Dr. Hunter examined flies caught in the plague wards and in the public mortuary in Hong-Kong during a plague epidemic; washings obtained from the bodies of the insects did not shew plague bacilli, whereas emulsions made from crushed-up flies shewed that 20 to 75 per cent were plague infected. He also found that plague flies were capable of infecting pieces of sugar over which they had been allowed to crawl. According to Dr. Hunter's evidence, plague bacilli may remain virulent in the intestine of the fly for forty-eight hours. In Manila, Herzog had negative results with cultures made from flies.

*Bugs.*—Experimentally, Dr. Nuttall found that plague bacilli can be recovered from the intestine of ordinary bed-bugs up to seventy-two hours after they had sucked the blood of rats suffering from plague, but it was impossible to transmit plague through the agency of these insects.

According to the testimony of the Austrian and German Commissions, it is unlikely that the transmission of plague takes place by the *Mosquito*. Dr. Hunter also failed to find bacilli in the body of mosquitoes even when they had been caught under the mosquito-nets of plague patients. In the Arthur Road Hospital in Bombay no transfer of plague from the sick to the healthy took place although the staff and attendants were constantly bitten by mosquitoes (Choksy (41)). Cultures made from *pediculi* obtained on the bodies of plague patients were negative in Dr. Hunter's hands. It was suggested by the Indian Commission that the unusually high incidence of plague among the Jains in India might be referable to transmission by pediculi. This race, as is well known, has an aversion to taking any life, and are, in consequence, infested with lice. In Manila, Herzog found plague bacilli in three lice (*P. capitis*) from a child dead of plague.

*Ants.*—Dr. Hankin believes that certain ants (*Monomorium rasilator*) can transmit plague, and they often succumb after feeding on plague rats.

*Cockroaches.*—Dr. Hunter maintains that this insect (*Blatta orientalis*)



may harbour plague bacilli and carry them for a considerable distance. He was able to recover cultures from the faeces of cockroaches.

**Fleas.** Since Ogata was able to infect mice by means of fleas which had sucked the blood of pest-infected rats, these insects have been the subject of much study. Simond especially developed the flea hypothesis of the transmission of plague, by trying to establish that plague rats are eminently infective when infested with fleas. He considered that when deserted by their parasites, rats cease to be dangerous, and that plague can pass from infected rats to other animals which have not been directly in contact with them or with their infected excretions. Loir went so far as to affirm that the fleas of rats are the main agents through which the disease is transmitted to man. Kolle and Nuttall obtained negative results in attempting to infect healthy rats with fleas obtained from plague-stricken animals. The Indian Plague Commission, from analysis of their data on the subject of fleas and plague, came to the conclusion "that Simond's proposition that suctorial insects play an important part in the transmission of plague from sick to healthy animals is so weak as to be hardly deserving of consideration." In recent years attention has been directed mainly to the question whether rat-fleas are capable of biting man. According to Galli Valerio (20) the common fleas (*Typhlopsylla musculi* and *Pulex fasciatus*) of the European rat do not attack man, and Tiraboschi is of a similar opinion. In 100 rat-fleas examined by Tidswell in Australia the incidence of the different varieties worked out as follows: *Pulex fasciatus*, 10 per cent; *Typhlopsylla musculi*, 8 per cent; *Pulex serrateps*, 1 per cent; and *Pulex pallidus* (*P. cheopis* Rothschild), >1 per cent. Of these the last, according to Tidswell, Gauthier and Raynaud, and Tiraboschi (94), can attack man. On ship-rats Tiraboschi found that 40 per cent of the fleas belonged to *Pulex murinus*. Both *P. murinus* and *P. pallidus* have been subsequently identified as *P. cheopis* Rothschild. In five experiments, Gauthier and Raynaud succeeded in conveying plague from rat to rat by fleas, and they also identified *P. pallidus* as present upon ship-rats. Ziroha states that even *P. uritans* and *P. serrateps* can retain plague bacilli in their bodies for seven to eight days. Captain Liston made the important observation that whereas in Europe *Pulex (Ceratophyllus) fasciatus* and *Typhlopsylla musculi* are the common rat-fleas, their place to the extent of 99 per cent is taken in the case of the Indian rat by a non-pectinated flea—*Pulex cheopis* Rothschild. Mainly through the researches of Major Lamb and Captain Liston, remarkable advances have been made in our knowledge of the flea-plague question during 1906. They have shown that the common Indian rat-flea (*P. cheopis*) can transmit plague from an infected to a healthy rat confined in close proximity, but protected in such a way as to prevent direct infection. In 55 per cent of the experiments healthy rats living in flea-proof cages contracted plague after receiving fleas collected from rats dying of septicemic plague in other cages. Experiments were also made in a series of cabins—so called "godowns"—constructed to imitate the conditions obtaining in the spread

of plague in man, guinea-pigs and monkeys being used. The essential differences in the construction of the various experimental "go-downs" were in the roofs, and especially whether the latter permitted rats to harbour in them, and whether light was permitted to enter or not. It was found that if fleas were excluded, the closest contact of plague-infected animals with healthy animals did not give rise to an epizootic among the latter. If fleas were present, an epizootic once started spread from animal to animal, the rate of progress depending directly on the number of fleas present. It is possible even for an epizootic of plague to start without any direct contact of healthy and infected animals. Infection may also take place without actual contact with contaminated soil, and that this is not due to aerial infection is shewn by the observation that animals, suspended a suitable distance above a soil grossly contaminated with plague-material and above plague-stricken animals infested with fleas, escape the disease. In plague-infected human dwellings, guinea-pigs can contract plague by becoming infested with plague-infected fleas, and this even in houses which have been disinfected. In some experiments animals, protected and unprotected against fleas, were exposed side by side in plague-infected houses with the result that the former remained free from the disease, while a number of the latter succumbed to plague. The dissection of seventy-seven fleas caught in infected houses shewed that twenty-three harboured *B. pestis*. These experiments, which have been published in the reports on plague investigations in India issued by the Advisory Committee appointed by the Secretary of State (1906), seem definitely to prove that under natural conditions the rat-flea is an important agent in the dissemination of plague. In the case of non-suctorial insects the dissemination of the bacillus may also be brought about indirectly.

**Spontaneous Plague in Animals.**—The plague bacillus frequently infects animals in natural conditions, the different groups attacked being widely separated from each other in the zoological scale.

*Primates.*—Epidemics of plague in monkeys occurred in the modern Indian epidemic in several places, especially at Hubli, Ankleshwar, Dharwar, and Kankhal. In Hardwar and the neighbourhood, Dr. Hankin isolated plague bacilli nine times in twenty-six cases. Both the highly susceptible langurs (*Semnopithecus entellus*) and the brown monkey (*Macacus radiatus*) succumbed to plague in the above places.

*Carnivora.*—Dogs and cats, especially the latter, occasionally develop plague. In India this was noted in Bombay, Karachi, Randra, and in particular at Ahmednagar, which was overrun with cats having open buboes in their necks. Dr. Ashburton Thompson saw spontaneous plague in cats in Sydney; Dr. Hunter the same in Hong-Kong. In the South African epidemics at Port Elizabeth, East London, and King William's Town, numbers of cats were proved to be suffering from plague (Mitchell).

*Ungulata.*—Cattle, sheep, goats, and horses are not known to contract plague spontaneously. Some have reported epizootics in pigs during



gue epidemics, but it is very doubtful whether the animals succumbed to genuine plague bacillus or to other forms of hæmorrhagic septicæmia.

*Rodentia*.—Bubonic plague has frequently been seen to affect rodents. As, a great plague mortality occurred among squirrels (*Sciurus palmarum*) in the Indian epidemic, especially at Hubli, Bangalore, Poona, and other places. Of special interest is a disease—in all probability true plague—which periodically decimates the Siberian marmot or tarbagan (*Arctomys m. er*) in Transbaikalia and Mongolia. This tarbagan plague was first reported by Beliansky and Reschetnikoff at Akscha on the Chinese frontier, the marmots shewing buboes in the axillæ and groins. It is believed that the tarbagan pest is highly contagious to man, and it was proved beyond doubt by Zabolotny that genuine bubonic plague is common in Eastern Mongolia. Rudenko also considers that tarbagan plague and human plague are identical; the susceptibility of the tarbagan to cultures of *Bacillus pestis* has been referred to on p. 373.

*Spontaneous Plague in Rats*.—By far the most important animals in this connexion are rats, the occurrence of spontaneous plague in which is one of the constantly observed features of the modern plague pandemic. As Abel (2) has shewn, the older literature, with the exception of notices by Avicenna and Orraeus, is practically devoid of references to spontaneous disease in rats preceding or accompanying bubonic plague in man.<sup>1</sup> Marked attention was directed to rats in 1894, when large numbers succumbed to plague in Canton and Hong-Kong (Yersin). The incidence of rat plague in India has been fully analysed by the Indian Plague Commission, the most striking outbreaks occurring at Mahlghala, Chak-Khalal, and Banga. According to Kitasato, rats were infected to the extent of 10 per cent in Osaka and 20 per cent in Kobe (Japan). Plague in rats was also seen in Formosa, Mongolia, and in the Philippines. In Africa vast plague mortality in rats occurred in Kisiba (Koch and Zupitza); to a less extent the same was seen in Alexandria (Gotschlich), Lorenzo Marquez (Vaz), Port Elizabeth (Blackmore), Durban and Maritzburg (Hill), Réunion (Maxse). In Australia human plague in Sydney was constantly preceded by rat plague (Thompson and Tidswell); in Europe plague epizootics in rats occurred in Oporto (Kossel and Frosch), in Naples (Santoliquido), and in the Odessa epidemic of 1901-2 (Rabinowitsch and Kempner, Skschivan). In South America a similar state of affairs prevailed in Asuncion

<sup>1</sup> In modern times the death of rats during or before epidemics of human plague was first noticed in India, viz. in Kumaon, 1834-35, by Gowan; in the Pali plague, 1836-38, by Forbes and White; and in Kumaon, 1853, by Francis and Planck. But there are records of rat-disease associated with human plague at least as early as the beginning of the seventeenth century in India, shewing that the phenomena were so striking as to arrest the attention of laymen as well as of physicians. Even in the ancient Hindu sacred book called *Bhāgavat Purana* (! ninth century A.D.), mortality among rats is referred to as a sign of a coming plague. There is an equally definite account of rat-plague in Yunnan at the beginning of the nineteenth century, and probably it was observed there much earlier. It is thought that the reference in the first book of Samuel (vi. 5) to "mice that mar the land" during the plague of "emerods," which afflicted the Philistines, is an indication of plague among mice or rats; though Biblical commentators give a different explanation.—J. F. P.

and in Rosario (Uriarte); likewise in Brazil (Havelburg) and in Peru. In several parts of India, however, no connexion could be traced between rat and human plague. The same applies to the Kolobowka epidemic (Tartakowsky). In the Glasgow epidemic in 1900 no plague could be found in the rats, nor was there any evidence that rats played a part in the dissemination of the disease. In 1901 and 1902, however, large numbers of plague-infected rats were found, and in several instances in houses in which human beings had contracted the disease in 1901. The species of rats which have been found to suffer from plague are *Mus decumanus* (brown rat), *Mus rattus* (black rat), and its variety *Mus alexandrinus*. There does not appear to be any difference in susceptibility among the various species of rats. Autopsies on plague rats shew the same changes as those met with in the experimentally produced disease. Of peculiar interest is the occurrence of *chronic* forms (*vide* p. 372) of spontaneous plague, which may possibly be the means of bridging successive epizootics (Hunter).

*Occurrence in Rats of Diseases resembling Plague.*—Since the modern outburst of plague spontaneous infections in rats have been frequently shewn to be due to bacilli other than *Bacillus pestis*, although the clinical and anatomical features led to the belief that the disease was genuine bubonic plague. Cases of this kind have been recorded by Danysz, Schilling, Aujezky, Kossel and Overbeck, Toyama, Neumann, Klein, and others. In most cases the bacilli found have been Gram negative and have shewn polar staining. The closest resemblance to *B. pestis* is shewn by Klein's *Bacterium bristolense*, which differs, however, in that abundant gas is developed in growths upon potatoes. Dr. Klein found it to be virulent for rats and guinea-pigs, except when applied cutaneously. *Bacillus pseudotuberculosis rodentium* (A. Pfeiffer) presents an extremely close resemblance to the plague bacillus (Galli-Valerio, Zlatogoroff, MacConkey), and can only be distinguished with the greatest difficulty. Mice are of much less importance than rats in connexion with the dissemination of plague; epizootics have, however, been observed among these rodents at Tai-ho-Kou (Formosa), at Jeddah, Alexandria, in South Africa, and in India at Bangalore, Porbandar, and other places.

Spontaneous plague has also been noted in the great bandicoot rat (*Nesocia bandicota*), in porcupines at Mysore, and in guinea-pigs at Sydney and Bangalore. At Knysna (S. Africa) veld rats (*Arvicanthus pusillus*) succumbed to plague in large numbers (Mitchell).

*Marsupialia.*—As a curiosity may also be mentioned the outbreak in the Zoological Garden in Sydney of spontaneous plague in wallabies and wallaroos (Ashburton Thompson).

*Variations in the Virulence of Bacillus Pestis.*—Considerable variations occur in the virulence of the plague virus on artificial media, some strains becoming rapidly attenuated, while others remain highly virulent for years. Thus, Albrecht and Ghon isolated from a rat a strain of plague bacillus which at the end of thirteen months was so virulent that  $\frac{1}{100000}$  of a loopful killed a guinea-pig with acute

pticæmia. The best method for preventing a spontaneous attenuation of virulence is to keep the cultures in sealed tubes and at a low temperature. Cultivation at the body-temperature sooner or later leads to a loss of virulence, a profound attenuation occurring if the bacillus be kept for long at 41° C. (Kolle). A convenient scale of virulence has been adopted by Kolle and Martini, the inoculations being carried out successively in the guinea-pig with 0.2 of a loopful of culture suspended in 0.5 of bouillon.

Non-virulent cultures—glandular swelling only ; slight emaciation.

Weak „ —death in 2-3 weeks, with chronic pest granulomas in viscera.

Medium „ —death in 8-10 days ; miliary nodules in spleen.

Highly virulent cultures—death in 4-5 days ; septicæmia ; no nodular formation.

#### *Attenuation of Virulence and Maintenance of Exalted State of Bacillus*

The plague bacillus can be exalted in virulence by passage in the bodies of guinea-pigs. The effect of its continued passage in rats is the subject of diverse opinion, Yersin, Calmette, and others considering that rat-passage produced attenuation. Drs. Hankin and Hinton (41) were unable to continue the passages through rats. With intermediary subcultures between the passages, Captain Douglas found great attenuation in the body of the rat. Otto (75) found that after twenty rat-passages the bacillus no longer produced septicæmia, but only an intoxication, the bacilli becoming localised in the lymphatic system without, however, being attenuated. The Advisory Plague Commission (1906) was able to infect twenty-six series of rats without recourse to special media, and was unable to find any alteration in virulence. It found that Bombay rats vary considerably in susceptibility, and that a considerable percentage of rats in India are immune to the cutaneous method of inoculation. Passage through a series of rabbits appears to maintain the bacillus for the rat (Otto).

**Plague Toxin.**—Experimentally a great deal of doubt exists in regard to the nature of plague toxin, and especially whether it is intra- or extracellular. Yersin, Calmette, and Borrel, Pfeiffer, Dieudonné, Dean, and the Austrian Commissioners, on finding that young plague-culture filtrates were toxic only in large doses, concluded that the poison was an endotoxin. On the other hand, Kolle maintains that when grown at low temperatures the plague bacillus produces an extremely unstable exotoxin within a few hours. As a result of his recent work, Kolle (54) is in agreement with those who regard the poison of the plague bacillus as being if not exclusively intracellular. With filtrates from young cultures he was unable to produce intoxication, notwithstanding the use of relatively large quantities (3 c.c. in rats). On injecting the bacterial bodies, on the other hand, a rapidly fatal disease was produced, with profound symptoms of intoxication, referable to the nervous and cardiac tissues. If the animals survived the acute stage they

succumbed later with marasmus, referable to parenchymatous degeneration of the heart, liver, and spleen. In general the filtrates increase in toxicity the older the culture, a maximum toxicity being obtained in cultures grown at  $37^{\circ}$  C. for three to four weeks. A peculiarity of filtrates from old cultures is that toxic symptoms come on at once and may cause death in one to two hours, a result due in all probability to secondary poisons, which have nothing to do with the primary pest toxin, the symptoms from which always make their appearance after an incubation-period, lasting six to eight hours. Pest serum has no effect in neutralising the secondary toxins. Besredka is of much the same opinion as Kolle. The toxicity of plague cultures grown on one and the same medium is very variable in its effects on rats, .1 c.c. being occasionally fatal, while at other times 3 c.c. may produce only transient symptoms (Douglas).

**Sites of Entrance of the Plague Bacillus into the Human Body.**—In considering the portals through which plague bacilli pass into the body of man the skin is of primary importance. The deadly effect of applying a living plague culture to a carefully shaved area of the skin of rodents proves that the bacillus can invade the body through minute breaches in the continuity of its surface. In all probability the same applies to man, although in the great majority of cases no definite primary lesion can be detected, and the bacilli first manifest their presence in the regional lymph-glands. That the bacillus can pass through the skin is shewn by the fact that the disease has in many cases been contracted by direct inoculation in the course of autopsies on plague patients. The Indian Plague Commission collected thirteen cases of this kind, and in only two of these (viz. Professor Sticker and Captain Leumann) was there a history of a primary vesicle or phlyctenule at the point of inoculation. To these two cases must be added that of Professor Aoyama. Apart from post-mortem wounds the German Commission reported eleven cases in which primary plague vesicles were noted. Simond reported sixty-one such cases, and the Indian Plague Commission observed four others. Although, therefore, the occurrence of a primary pest lesion must be looked upon as rare, it is to be noted that the proportion in which certain groups of lymphatic glands are infected is almost directly in proportion to the skin area which is drained by the lymphatics passing to these glands. Thus, the area of skin surface draining into the lymphatic glands of the neck is approximately 1260 square centimetres, that into the glands of the axilla about 3244, and that into the glands of the groin about 6260 square centimetres, the areas having a proportion to each other of about 1 : 1.8 : 5. From the statistics of Bombay, Punjab, and Karachi hospitals (5442 cases), the proportion of primary cervical, axillary, and inguinal buboes was 1 : 1.3 : 5.8. Everywhere a primary pest lesion occurs at the point of the inoculation it is frequently preceded by general symptoms, a point of importance in estimating the manner in which the bacillus invades the body.

**Mucous Membranes.**—The frequent occurrence of buboes under the e.

and about the angle of the jaw may be taken as evidence that the plague bacillus can penetrate through the mucous membranes of the nose, mouth, or pharynx. The same applies to the conjunctiva. A patient with pneumonic plague accidentally coughed into the eye of a nurse in the hospital at Parel. Conjunctivitis followed, with a plague bubo below the ear on the affected side. A similar case was noted in Hong-Kong.

Cutler reported the case of a boy who had a lesion on the dorsal surface of the glans penis. Plague bacilli were found in the lesion and in the buboes which developed in both the groins.

In regard to the statement that plague bacilli enter the body through the gastric or intestinal mucous membrane, the Indian Plague Commission were unable to obtain any trustworthy evidence. Feeding experiments have always been found to be uncertain, and it is probable that many animals supposed to have been infected through the stomach or intestine have in reality been infected through the nasal or pharyngeal mucous membrane. Wilm, however, held that the disease could be contracted through the alimentary wall, and Dr. Hunter is of opinion that this is a common method of infection. That in many cases the mucous membrane of the alimentary canal is found post-mortem to be studded with hemorrhages is, however, no evidence that the plague bacillus gained entrance by this route. In the case of rats, Dr. Klein shewed that in whatever manner the animal is infected, the intestines and mesenteric glands always participate in the disease.

*Respiratory Tract* (except nose and mouth).—In cases of primary plague pneumonia there can be no doubt that the bacilli may gain entrance by means of the inspired air. Such cases are characterised by great infectivity, and frequently disseminate the disease. This occurred in the laboratory outbreak in Vienna, the attendant Barisch, Dr. Muller, and Nurse Fecha all succumbing to pneumonic plague conveyed from the one to the other. The factors which predispose to the development of lung plague are not fully worked out. From the experiments of Martin it is probable that the bacillus is exalted in virulence in its passage from lung to lung. Other microbes, such as the pneumococcus, may also be associated with the plague bacillus, and possibly affect its virulence.

**Escape of Bacilli from the Body.**—In ordinary bubonic cases there is usually a short period when the bacilli are shut off from the surface. In a great many cases, however, the blood invasion takes place at a very early date, and from this time onwards the bacilli may escape from the body. By becoming lodged in the capillaries of the skin and mucous membranes, they may make their exit from the body. In the case of the respiratory organs, when there is primary or secondary plague pneumonia they pass out in immense quantities in the sputum. To a certain extent this also occurs in ordinary bubonic cases with blood infection. The bacilli may be conveyed to the surface of the intestine and pass out in the feces, although this has only rarely been demonstrated experimentally. Conveyance of the bacilli to the kidneys and escape by



the urine is also proved. In sixty examinations of the urine the Indian Plague Commission found plague bacilli three times. In the case of hæmorrhages from the cutaneous or mucous surfaces of the body the bacilli may make their exit in large numbers.

*Infectivity of Patients convalescent from Plague.*—The infectivity of plague patients who have recovered from the acute stage of the disease is especially marked in the cases of suppurating buboes and in cases with bacilli in the sputum or saliva.

It is generally difficult to find bacilli in buboes which have been suppurating for some time. The German Commission had two positive results out of sixteen cases. The Austrian Commissioners were more successful (seven positive in ten cases) in so far that they isolated living bacilli on the nineteenth and twentieth days, and in one case as late as the fifty-second day. Vagedes, in the Oporto epidemic, recovered bacilli from a pelvic abscess two and a half months after the attack of plague was over.

Bacilli may persist in the sputum and saliva of patients for long periods after recovery from plague. Thus, in two pneumonic cases Gotschlich found the bacillus twenty and forty-eight days respectively after the temperature was normal. Vagedes recovered living bacilli from sputum seven weeks after the disease.

**Bacteriological Diagnosis of Plague.**—During an epidemic of plague in man it may be justifiable to base the diagnosis on clinical evidence alone. In all other cases a bacteriological examination is imperative, and should be conducted by a trained bacteriologist in a suitable laboratory. The diagnosis rests on the demonstration of the bacillus in the suspected material, either by microscopic examination, or in cultures on gelatin or agar plates. Inoculation of the suspected material, or cultures from it, should also be carried out on susceptible animals, such as rats and guinea-pigs. Subcutaneous or intraperitoneal injection is suitable only in cases in which the primary material is not extensively infected with different microbes, or where pure cultures are used. In all other cases the cutaneous application of the infective material is to be recommended. If the accurate diagnosis be of great importance—as is usually the case in non-epidemic periods—several animals should be employed. As death may not take place for some days, it has been suggested that the buboes should be punctured, the juice being examined microscopically or by other tests. The buboes are frequently, however, very small, so that their puncture is by no means easy. It is preferable to kill the animal on the second day, and to dissect out the buboes carefully for further examination.

If there is any doubt as to the identity of the microbe found either in the primary cultures or in the inoculated animals, it should be subjected to all the known tests, including the agglutination reaction with plague immune serum, the suspected case from which the material was primarily obtained being kept under careful observation. In living patient material may be obtained from the interior of the bubo

injection with a sterile hypodermic syringe. In the early stages of the bubo plague bacilli are present in large numbers, whereas later on, especially in the event of suppuration, they may be sparse, and their presence may be obscured by other microbes, which have invaded secondarily. In very severe cases plague bacilli may be obtained in blood films, and especially in thick drops of blood which have been allowed to dry upon slides. Before staining such preparations it is necessary to get rid of the haemoglobin by soaking the slides in distilled water. The most certain method of demonstrating bacilli in the blood is, however, to take quantities of 2-5 c.c. directly from the median basilic vein, and to dilute it at once in about 100 cc of bouillon. From the mixtures, agar or gelatin plates can then be made. In the case of the sputum in primary pest pneumonia, pest bacilli are usually but not always present in immense quantities, and can often be detected by the microscope alone. Secondary microbes may, however, mask the microscopic picture, and cultures and inoculations must be carried out. In such cases the cultures on gelatin at 20 C. are particularly appropriate, as many of the bacteria which complicate a pest pneumonia do not grow readily at room temperature. In order to save valuable time, cutaneous inoculation directly from the sputum should be employed.

In searching for plague bacteria in urine, this fluid should be collected under aseptic conditions, and it is to be noted that cultures from urine are often slow in growth.

Cutaneous inoculation of the guinea-pig or rat is the only means of satisfactorily demonstrating pest bacilli in faeces, and in any case one must be prepared for frequent disappointments.

*Agglutination.*—Wyssokowitch and Zabolotny were the first to draw attention to the presence of specific agglutinins in the blood serum of patients suffering or recovering from plague. This has unfortunately, however, proved a very unsatisfactory test clinically, as the agglutinin formation is usually slight (1:5 to 1:10), is often late in appearing, and may be entirely absent in cases of undoubted plague. It has also been found experimentally that a great deal depends on the virulence and other characters of the strain of culture used. Where employed, the test should be carried out by the macroscopic method in small tubes, very carefully prepared emulsions of plague bacteria being used.

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**Geographical Distribution of Endemic Plague.**—In discussing the existence of plague as an endemic disease, it is necessary to take into account its geographical distribution, and to some extent its history—together with the associated physical and social conditions. The localities where it is now known to occur, or to have occurred within the last thirty or thirty-five years, without being obviously imported from any other centre, are as follows:—

(1) The district of Benghazi (the ancient Cyrenaica), in the province of Tripoli, Northern Africa, last definitely recorded in 1874: perhaps later.

(2) The district of Azir or Assyr, in South-Western Arabia, bordering on the Red Sea, as lately as 1889.

(3) A large area in Asia, comprising Persian Kurdistan and adjacent parts of Persia, Turkish Kurdistan, and parts of Irak or Mesopotamia on the banks of the Tigris and Euphrates, including Baghdad. The chief endemic centre of this area is, according to Tholozan, in the mountains of Kurdistan. From this area it has extended to Northern Persia on the

shores of the Caspian (Resht) in 1877, to Baku on the western, and Astrakhan on the northern shore of that sea; and up the Volga to the village of Vetlanka and its neighbourhood in 1877-79.

(4) The districts of Kumaon and Gurwhal in the north-west of India, on the slopes of the Himalayas, as lately as 1897.

(5) In Southern China, the mountain district of Yunnan, from which epidemics extend to the seaport Pakhoi on the Tonkin Gulf. Apparently by extension from Pakhoi, plague has invaded Canton and Hong-Kong in Eastern China, and thence obtained an almost world-wide distribution.

(6) Central Africa, in a district of which the endemic centre appears to lie about Uganda, just under the Equator.

(7) A district of Siberia, in the Trans-Baikal province, where a disease apparently identical with plague is sometimes communicated to man from a rodent animal, the Tarbagan marmot (*vide* p. 377). It is almost certain that there are other centres of plague in Siberia and Central Asia which at present cannot be clearly defined.

The localities above named appear to be independent endemic centres of the disease, since no communication can be traced between them.

These localities are all in the temperate zone, with the exception of the Azir district, which lies just within the tropics, and Uganda, which is just on the Equator; but they have hardly another physical feature in common. Plague prevails in Benghazi on a rocky plateau overlooking a marshy district liable to inundation; on the banks of the Tigris and Euphrates, and on part of the shores of the Caspian in low and marshy situations. But the mountains of Kurdistan are 5000 to 6000 feet high; and the Himalayan seat of the plague approaches 7000 feet above the sea; while in Yunnan the disease is said to occur only at elevations of from 1200 to 7200 feet. These data shew the old belief that plague prevails only in marshy and malarious districts, or has any predilection for the mouths of great rivers, to be entirely unfounded. Indeed the most persistent foci of plague now known are in mountain districts. The social conditions of these regions are, however, more uniform, and will receive special consideration later.

**Two Strains of Plague.**—Of these endemic seats of plague (1) and (2) are unimportant, while (6) and (7) are as yet imperfectly known. The remaining three only are of importance in relation to the persistence and spread of plague. No. 3 comprises a large district, various parts of which have been frequently visited by plague, but in which the most permanent endemic focus appears to be in the highlands of Kurdistan and part of Persia. It has made frequent extensions into Persia, Armenia, Irak, Turkish Arabia, the shores of the Caspian, and rarely the Black Sea, while in former days it supplied the epidemics of plague in the Levant. For the sake of a name this may be called the Western Asiatic or Levantine plague. (4) and (5), though far apart, may be taken together, since the mountains of Yunnan are an extension eastward of the great Himalayan range, and the disease in these two centres appears to be so

identical in its natural history. These two constitute the Himalayan and Chinese, or together the Indo-Chinese, centre. It is the Yunnan plague which has become so widely diffused, not only in the far East, but nearly all over the world, and exhibits, wherever it takes root, the features of the original plague of that region.

It is important to observe that the disease in the two great centres above indicated, and their secondary foci, are not precisely alike, but present variations not constituting two distinct varieties, but different *strains* comparable to the different strains of yeasts which produce different kinds of fermentation.

The Eastern Asiatic strain is distinguished by—(1) The frequent occurrence of epidemics of *Pestis minor* or mild plague. (2) The absence of any observed connexion with the epizootic disease in rodents. (3) More frequent self-limited epidemics. (4) Consequently less marked power of extension; for the Eastern Asiatic epidemics have not, in modern times, travelled very far. (5) On the whole less virulence and a lower case-mortality. The mortality at Baghdad and other places in Irak was from 55 to 52 per cent, only in isolated epidemics rising to 90 per cent or more. In Egypt, before the final extinction of plague in the last century, it was as low as 33 per cent. In India, on the other hand, the general case-mortality, according to Dr. Simpson, was 70 to 85 per cent, in Hong-Kong 89 to 96 per cent, though in Europeans it was much less; and less also in other countries where the plague has been introduced. (6) The pneumonic form with hæmoptysis is decidedly rare though not unknown. There do not appear to be any marked differences in the symptoms, but the old Western Asiatic plague has not yet been examined with the same scientific accuracy as recent epidemics of the Indo-Chinese plague. At present there are no observations shewing any difference in the bacilli.

The characters of the Indo-Chinese plague are, as contrasted with the other form—(1) An almost invariable connexion with great mortality among rats, and less frequently among other animals. (2) Less frequent occurrence of epidemics of *Pestis minor*, though it is possible that further observation may shew these to be commoner than has been supposed. (3) Remarkable power of extension, as shewn in its spread over a large part of India and conveyance to many other countries. (4) In general, intenser virulence and higher case-mortality. (5) The pneumonic form, accompanied by hæmoptysis, is much commoner.

Further observations may shew that some of these points of difference between the two strains are less distinct than they now appear, but the striking contrast in the relation of the two forms of plague to disease in rats will always remain a historical fact, as has been pointed out. These differences confirm to some extent the views of the great epidemiologist Hirsch, who regarded the Indian plague as a variety of the disease distinct from the Levantine or Oriental form, being characterised especially by the occurrence in the former of pneumonia, which he justly remarks is very rarely recorded in the latter form. But after



oting the prevalence of pneumonia and hæmoptysis in the epidemic of 'etlanka, Hirsch abandoned the idea of two varieties of plague, which, owever, has still much to be said in its favour. It is important to remember that as the plague now widely distributed over the world is ne Yunnan plague, all modern observation and research on the subject ince 1894 have dealt exclusively with this variety of the disease.

*Endemic Plague in Relation to the Soil.*—In places where plague has een long established there are certain relations which connect it with he soil. It persists in certain regions, not distinguished by physical haracters from others where it never occurs. Within these regions t will recur year by year or in successive epidemics, at the same spots, ven in the same houses. Francis observed at Kumaon two villages on he same mountain, with the same aspect, scarcely 500 yards apart, of which, at every visitation of plague, one always escaped while the other suffered. In cities where a notable part of the population lives on the water in boats and barges, it has more than once been noticed that such persons have entirely escaped the plague. It was so in London in 1665; and also recently in Canton, where 250,000 people live and sleep on the water. Another point bearing in the same direction is the slow pace with which plague spreads on land, quite unlike those diseases like small-pox, measles, etc., which are propagated by contagion passing through the air. Boghurst states that in London in 1665 the plague took six months to pass from Westminster to Stepney through the City. Observations on the occurrence of plague in rats and other animals living under ground, point in the same direction. These and other considerations shew that there is some close connexion of the plague virus with the soil, and the view that plague is originally a 'soil disease' is suggested. This has been the popular belief in many parts of the world, and was dimly perceived by many old physicians (*e.g.* Boghurst in the seventeenth century) though clogged with other quite untenable hypotheses. In the eighteenth century and later the strong belief in contagion banished the soil hypothesis, but observations in India revived it. C. R. Francis explained thus the origin of plague in Kumaon in 1853. Liebermeister suggested that it was probably a 'miasmatic' as well as a contagious disease, and it was provisionally adopted by myself in the *Encyclopædia Britannica* and elsewhere. Dr. Creighton has brought it into connexion with Pettenkofer's 'soil-water' hypotheses. It is not refuted or weakened by the demonstration of the bacillus as the cause of plague, but recent researches make it possible hat the virus persists in animals living under ground rather than in the oil itself. The question of the presence and behaviour of the bacillus n the soil under varying conditions is dealt with on p. 369.

*Relation of Plague to Climate and Temperature.*—Its geographical istribution shews that plague is not exclusively, or even predominantly, tropical disease. It prevails widely in the temperate zone; even its most permanent endemic seats in India and China, the Himalayan illages and Yunnan, are outside the tropics, and its greatest epidemic

prevalence in Bombay, Bengal, and other parts to which it has spread has been on the margin of the tropical zone, a few degrees south of the tropic of Cancer. The presidency of Madras has been conspicuously less affected than other parts of India, and its southern provinces have shown only a few sporadic, probably imported, cases. The only endemic centres strictly within the tropics are Assyr in Arabia, and Uganda in Central Africa. In South America the places where imported plague has been most conspicuous Santos, Asuncion, Rosario are outside the tropical zone. Destructive epidemics have occurred even amid the snows of northern Russia, at St. Petersburg and Moscow. The general conclusion seems to be that while plague may prevail in almost any climate, its seats of predilection are in warm temperate regions, or the borders of the tropical zone. This distribution appears to be determined by the relations of plague to the temperature of the air.

*Seasonal Relations of Plague.*—In places where plague is endemic, it breaks out from time to time in an epidemic form. The precise laws governing epidemics of plague are not known, but they have an evident relation to seasonal changes. In northern countries epidemics generally begin in the spring, increase during the summer without being checked by heat, and reach a maximum about September. In the winter the disease mostly dies out or lies dormant till the following spring. There have, however, been epidemics which have continued through the cold even of a Russian winter (Moscow, Lower Volga, 1878-79). In Egypt, when the plague was prevalent there, epidemics used to begin in autumn, continuing through the winter, but ending abruptly about midsummer, when the hot winds from the south began to blow. In India the epidemics have mostly begun about October, continuing through the winter, reaching their greatest intensity in March or April, and subsiding in June, so that a comparatively low mortality, but not an actual cessation, occurred in July, August, and September. In Australia the relation of plague to the seasons has been analogous to that in Europe, *mutatis mutandis*.

The general conclusion from these observations is that summer heat in hot climates and winter cold in temperate climates checks or extinguishes plague, temperatures below 50° F. or above 85° being decidedly unfavourable to it. In Mesopotamia a temperature of 86° checks an epidemic, while one of 113° absolutely stops it. In Hong-Kong a temperature above 83° caused a decline of the epidemic till the following spring. In Bombay there is a fall in the mortality when the temperature is 82° or even 80°.

In Kumaon, Francis found the epidemic to continue when the temperature was 85° or even 105° in moist air, but a lower temperature would check or stop it if the air were dry. Dr. Simpson states that in Sind small epidemics have occurred with an air temperature between 110° and 120°, but they are very rare.

Epidemics of plague may last from three to eight months, but the longer period is exceptional. There is no obvious cause except seasonal



ranges for the termination of an epidemic. It is remarkable, however, that when the plague begins to decline, its infectivity as residing in houses, bedding, clothing, or other objects which have been in contact with the sick, is rapidly or almost suddenly lost, so that healthy persons may almost with impunity return to infected houses and sleep in infected beds. This was observed in the London Plague of 1665, and also repeatedly in Constantinople, Egypt, and the Levant, when the plague prevailed in those places, as well as at Bombay in 1897-98. No precise explanation can be given of this phenomenon.

*Periodical Recurrence of Plague.*—While remaining fixed in one spot, plague varies very much in prevalence and intensity. The disease is particularly liable to recur in periodical outbreaks; and in the countries affected popular belief has sometimes assigned a definite number of years, such as seven, for the interval. There is, however, no such regularity; sometimes a great epidemic is followed by several years of apparent immunity, sometimes the disease recurs several years in succession. The interval of apparent health is probably often filled, not so much with sporadic cases of severe plague, as with minor plague.

The causes of the development of minor into severe plague, and of the production of an epidemic, are very obscure. For various reasons it cannot depend upon the number of susceptible persons in the population; the causes must be physical, affecting the biology of the plague bacillus whether in or out of the body. The best-established fact is that epidemics in temperate climates have often (but not constantly) been preceded by a long drought. In hot climates, as in Bombay, a recent wet season seems to favour the production of an epidemic. Epidemic diseases among animals, failure of crops, great abundance of lower forms of life—such as flies—and numerous other physical incidents, have been also described as preceding or accompanying plague, but are of little moment. More important are social conditions. Many epidemics of plague have followed on famines, wars, and other calamities, which produce destitution and lowered state of health. Other fevers have sometimes been observed to prevail at the same time.

*Conditions favouring the continued Existence of Plague.*—It has been seen that no physical conditions, except temperature, have much effect on the prevalence of plague. But certain social conditions have a great influence, and seem almost indispensable to an endemic seat of the disease. The first of these is uncleanness. All the localities in which plague flourishes are conspicuously filthy. The villages in Mesopotamia were in an incredible state of dirt (Colvill). The sufferers from Indian Himalayan plague were filthy beyond conception (Francis); the habits of the poorer classes of Chinese in Hong-Kong and Canton are notoriously of the same kind. A soil contaminated with faecal discharges and decaying animal matter of all kinds appears to be an essential condition for the vitality of the virus. Among other causes of contamination must be placed cadaveric infection from bad customs of burial. This was notably observed in the Indian seats of plague, where the rocky nature

of the soil offers obstacles to efficient burial; in Yunnan also, and formerly in Egypt. Dr. Creighton regards this as the dominant cause, but the general bearing of testimony hardly confirms his opinion. The burial of those who die of the plague among or within dwelling-houses has of late, however, been a potent means of continuing the infection; such burials contain bacilli in enormous numbers, and contagion from dead bodies is undoubtedly possible. Overcrowding of dwelling-houses (not necessarily correlative with density of population) and absence of ventilation are also powerful contributory causes. These conditions are conspicuously prevalent in Hong-Kong and Canton; also in Bombay and other Indian cities. But of all social conditions poverty and general social misery seem to be the most influential. The poor are always the chief, and sometimes almost the only sufferers, as shewn by such epithets as *misere morbus*, or the "the poor's plague," often given to the disease.

But since destitution and uncleanness are prevalent in so many parts of the world where plague has never been heard of, these must be regarded as favouring, or perhaps essential, conditions for the disease rather than as accounting for its origin.

*Plague as a communicable Disease.*—Unlike true soil diseases—such as tetanus—there can be no doubt that plague is communicable, both from the sick to the healthy, and from an infected place to one previously uninfected; but the extent and nature of this communicability have been the subject of active controversy.

Communication of the ordinary form of plague from the sick directly to the healthy is rare and does not take place especially by contact, as was formerly believed (hence the word contagion, with its false connotations, is better avoided), but by the atmosphere of the sick-room or of the house itself, or by objects in the house; this may be largely if not completely, obviated by abundant ventilation. It may be difficult to say in some cases whether the infection is acquired from the patient or from the house; but it is pretty clear that communication of plague from one person to another in the open air, or by casual meeting, is very rare, if it ever occurs. The pneumonic form of plague, on the other hand, is extremely contagious. The transmission of infection by clothing, bedding, or other objects, that is, in the old phrase by *fomites*, cannot be questioned, though many exaggerated statements have been made on the subject. Recent observations on the subject do not shew merchandise to be an important vehicle for transmission of plague, except corn, and this only through its association with rats, as was seen in South Africa, at Cape Town, and in Elizabeth, where the plague was brought by fodder and grain from South America. In Japan infection was traced to bales of cotton. "gunny bags" used for holding grain were a means of infection in India. In Egypt rags were suspected.

Those who, like the French physicians in Egypt, denied contagion altogether, did so chiefly on the ground of their own personal immunity, though they attended thousands of patients, and performed many pro-

ortem examinations. One of them, Bulard, even wore the clothes of a patient who had died of plague, and Clot Bey tried in vain to inoculate himself with matter from a pestilent bubo. But an English physician, White, lost his life by an inoculation experiment. Many similar negative instances are on record ; but much negative evidence is not so conclusive with regard to infection as a few positive cases. On the whole, the truth appears to be that during different epidemics and at different ages of an epidemic, plague differs much in its contagious property, as does in its virulence ; so that, broadly speaking, it is highly communicable at some times, and very slightly so, if at all, at others.

In explanation of cases where communication cannot be traced, it should be noted that, besides rats and the like, domestic animals may convey germs of disease. It has been thought that lice, bugs, fleas of various species may convey the infection, but this supposition, though in some cases sufficiently proved, has not been shewn to be the usual or a frequent mode of communication (*cf.* p. 375).

Transmission of plague from one place to another not previously infected must also be regarded as well established ; though, doubtless, this may have been wrongly assigned as the cause of purely local outbreaks. That this is possible by means of infected ships is clearly proved by the records of the Quarantine at Marseilles (quoted by Prus), when in several instances the infection was, so to speak, caught on the sieve—that is to say, the infected ships gave rise to cases of plague within the quarantine station, of which some were fatal. Of late years numberless instances have occurred of the transmission of plague from Hong-Kong and other Chinese ports to many parts of the world, and from the secondary centres thus established back again to Europe and to Africa, so that at the present time this mode of transmission constitutes a serious danger. The most important means of transmission is through the medium of ship-rats affected with plague. Mortality among rats on board ships leaving ports infected with plague has often been observed. In ships thus infected cases of plague have sometimes occurred among the crew or passengers, but not always, for the disease spreads from rats to men only by casual opportunities ; but persons employed in unloading the cargo have been infected, and rats leaving the ship have carried the infection inland. By this disease of rats plague has been conveyed on longer voyages and over greater distances than would be possible if the infection were carried by cases of human disease only. For human beings sick of plague would either die or recover before the end of a long voyage. Transmission by land for short and sometimes considerable distances, is also well established. In the London Plague of 1665, towns and villages in communication with London became affected, though they were previously healthy, and had not suffered from plague for many years, if ever. The infection is doubtless generally conveyed by persons either affected with the disease or in the stage of incubation. Such persons convert the house they occupy into a focus of infection, till possibly the virus passes either into the soil directly, or into animals such

as rats; and thus a permanent source of infection is established. Conveyance by means of infected objects is doubtless possible, but probably much rarer. In India there were several well-established instances of conveyance of plague to cities and villages by human intercourse quite independently of rats. At Satara the first epidemic was produced by human intercourse alone, whereas in 1898-99 rats were affected before human beings (Thomson). In the Punjab forty-seven out of sixty-three villages were infected by the arrival of infected persons. In some the infection was brought by a single person affected with mild plague (James). But it has happened that the infection thus brought has first fallen upon the rats, and afterwards attacked human beings.

With regard, however, to this mode of transmission, it should be observed that, according to old and sound tradition, the plague does not spread when it is sporadic, but only when it is in an epidemic form. Furthermore its diffusibility varies as much as its contagiousity in the narrower sense, being very marked in great epidemics, very slight or self-limited in others. Many epidemics have burnt themselves out on the spot, or travelled but a few miles; others have spread over whole continents. Generally successive epidemics, if unchecked, cover each time a somewhat wider area.

The rate of extension is also variable, but is generally slow. Plague has taken weeks or months to pass from one side of a city to another; it creeps along from point to point, so as to be compared by some to a drop of oil on paper. Such gradual extension suggests the slow progress of a virus in the soil itself, and probably that is in some places the explanation; but, obviously, only transmission through short distances can be thus accounted for. The migration of rats affected with plague may in some cases be the explanation.

Transmission by the air cannot be said to be impossible, and was once much dreaded; but while this may be possible through distances measured by yards, it can hardly be so through distances measured by miles (*cf.* p. 369).

**Morbid Anatomy.**—Full accounts were made up by the French physicians in Egypt in 1834-35 according to the pathology of that day, and agree in the main with the recent much more elaborate descriptions. A very characteristic feature is that of engorgement and hæmorrhage, the extravasation from the veins affecting nearly every part of the body (Simpson). The bodies of plague patients do not undergo very rapid decomposition, except in the septicæmic form. The central nervous system, especially the brain, is deeply congested; the brain substance in some instances is softened, and the blood-vessels, especially the veins, much engorged. The lungs are much congested, and œdematous especially in their posterior parts, with small hæmorrhages in their substance and on the surface; as well as on the costal and diaphragmatic pleuræ. The larynx, trachea, and bronchi shew catarrhal inflammation, with œdema of the glottis in some cases. Broncho-pneumonia is a common complication. It is described by Dürck as

confluent lobular pneumonia or lobular hepatisation. Embolic abscesses are found in some cases. The pericardium contains an excess of fluid, frequently blood-stained, with ecchymoses on both surfaces. The right side of the heart is dilated with black, imperfectly coagulated blood, and the whole venous system is engorged. The veins of the trunk when cut open display numerous small hæmorrhages, which in the vicinity of a bubo become hæmorrhagic patches of considerable size (Simpson). The heart substance is pale, and sometimes softened. The stomach and small intestines may contain blood-stained fluid, sometimes actual blood, the surface shewing intense venous congestion; but Mr. Cantlie, in Hong-Kong, found no congestion of these parts. In a few cases superficial ulcerations have been noted. The Peyer's patches are not generally affected, but in some cases are swollen and ulcerated. The large intestine is comparatively normal. The peritoneum is described as shewing great vascular congestion, with hæmorrhages into the mesentery. The mesenteric and retroperitoneal glands are generally enlarged and sometimes shew much inflammation and hæmorrhagic infiltration, which Dr. Simpson says was especially noticeable in Hong Kong. The liver was found enlarged by the French pathologists, sometimes considerably, but Mr. Cantlie found no notable enlargement: its substance is pale and anæmic, and presents the appearance of cloudy swelling. Embolic abscesses may occur (Durek). Hæmorrhage, interstitial or superficial, is found occasionally. The spleen, according to all observers, is greatly enlarged. The kidneys are sometimes enlarged, and occasionally present hæmorrhagic patches; Mr. Cantlie describes their histological appearance as being that of cloudy swelling. The general appearance is like that of the scarlatinal or septic kidney, and special changes occur in the glomeruli, due to the passage through them of plague bacilli, which are also found in the urine (Durek).

The one characteristic sign is inflammation and swelling of the terminal lymphatic glands, a condition always present even when the external glands are not notably enlarged. All groups of lymph-glands may be affected so as to form continuous chains, the cervical being united with the mediastinal and bronchial; the inguinal with the groups surrounding the iliac vessels and aorta, and with the pelvic glands, and so on. The mesenteric glands are least frequently affected. Agglomerated glands may form masses weighing as much as two pounds. In substance they are sometimes red, congested, and hard, sometimes soft and discoloured, sometimes breaking down into a pulp. The surrounding tissue is infiltrated with serous fluid, and often shews extravasation of blood.

It is evident that, apart from the condition of the lymph glands and the diffuse hæmorrhage, there is nothing distinctive in the morbid anatomy of plague. Sir T. Fraser remarks that the vascular changes and pervading tendency to hæmorrhage closely resemble the results of the toxæmia set up by certain kinds of snake poison.

**Forms of Plague.**—It has been generally recognised that plague



occurs in two forms distinguished chiefly by their severity, the one having been called *Pestis minor*, or mild bubonic plague, the other, *Pestis major*, or severe bubonic plague, which present different forms or types. But recent observers prefer to classify the cases under three main heads: viz. Bubonic, Septicæmic, and Pneumonic, according as the glands, the blood, or the lungs are mainly affected. These three forms are not absolutely distinct; they may be combined, or one form may pass into another, but other special symptoms are generally associated with each variety. The mild or minor form seems, however, to deserve special mention, and thus we have four varieties or forms:—(1) Mild bubonic, (2) Severe bubonic, (3) Pneumonic, (4) Septicæmic.

**I. Mild Bubonic Plague or Pestis Minor** has received of late years less attention, because it does not form a part of the severe plague epidemics, and does not seem to be so characteristic a form in Indian or Chinese plague as in the other. But in various parts of the world it has been observed to prevail unchanged for periods of weeks or months. It is often the precursor of severe epidemics, and in such cases the increase in severity is sometimes gradual, but more often a sudden development into the severe form occurs. The bacillus has been found in mild plague by recent observers. This form was observed in Mesopotamia, preceding severe epidemics in the years 1873-77; and in the city of Astrakhan in 1877, the year preceding the severe outbreak of 1878-79 at Vetlanka in that province. It also occurred in London in 1664, the year before the great epidemic. It may also, in plague countries, follow a severe epidemic. This form is distinguished from the severe bubonic form by the facts that it is never, or rarely, fatal; that no contagion is observed, and that it is not transmitted from one place to another, at least in the same form. Mild forms of plague have also been observed in India and China prevailing as epidemics, but perhaps with less distinctness than in the Western Asiatic seats of plague. Further observations are, however, required. Since it causes only a slight or no mortality, this form of plague has often been overlooked or misunderstood.

In some countries the prevalence of a disease characterised by glandular swellings without fever has been observed to precede epidemics of definite plague. This happened, for instance, in Egypt 1834-35, where it was explained as due to an *aura pestilentiæ*; in Baghdad 1867, and elsewhere in Mesopotamia ten years later; in Hong-Kong and Southern China before the great epidemic (Cantlie). This affection has also been called *febris intermittens bubonica*, but the epithet *intermittens* is inappropriate. Probably these were all instances of mild plague; but there are no records of examination for bacilli.

**II. Severe Bubonic Plague.**<sup>1</sup>—*Incubation.*—The latent period between the reception of infection and the commencement of symptoms is imperfectly known, but appears to be generally from three to five or at

<sup>1</sup> In this summary the accounts given by Dr. Cabiadis and Mr. Colvill of plague in Irak have been combined with the more important and more detailed later observations made in India, China, and other parts.

most ten days. Observation for about eight days may therefore be taken as sufficient to shew whether a suspected person is or is not infected, but in some cases this period may have to be prolonged.

The symptoms of plague vary much in their intensity and relative frequency in different epidemics; but the order in which they present themselves and the general course of the attack are tolerably uniform.

*Prodromal Stage.*—Often the onset is quite sudden; but when preliminary symptoms (prior to the coming on of fever) are observed they are as follows.—The nervous system is chiefly affected. There is severe headache, vertigo, staggering gait, and appearance suggestive of drunkenness passing into lethargy. Colvill says "The patient appears absent-minded, moves along speaking to no one, enters his house mechanically, unlocks the door, and drops on to his bed, as if in despair or wandering in his mind." The pallid face, the injected eyes, the vacant or stunted expression of countenance, with inability or refusal to answer questions, often enable an experienced eye to make the diagnosis. With these are associated the usual symptoms of acute febrile disease, pains in the limbs, extreme muscular weakness, and intense malaise. The tongue at first is thickly coated on the dorsum, the edges being red, later it becomes extremely dry and of a mahogany colour. Bilious vomiting or hæmatemesis are occasionally the initial symptoms. The prodromal stage, when present, may last a few hours or a day, rarely longer.

*Febrile Stage.*—Immediately after the above symptoms, concurrently with them, or sometimes from the beginning, high fever comes on, ushered in by a prolonged rigor or repeated shiverings. The temperature may rise rapidly to 102°, 104°, or even to 107° F and higher. The pulse is always rapid, from 90 to 120 or 130. The maximum is usually attained on the evening of the second or third day; sometimes on the first, rarely on the fourth day. It is described as sometimes very small and thread-like, at other times not especially weak. Mr. Cantlie speaks of it as very variable in force, frequency, and character. The skin is at first extremely dry, not always very hot to the touch. There is excessive thirst, with a sense of burning in the throat and stomach. Constipation is the rule during this stage. Nausea or vomiting is sometimes observed. From the extreme weakness the decubitus is dorsal. The nervous disturbances are mainly those already described; sometimes they pass into active delirium, more often into lethargy and coma. Insomnia may alternate with drowsiness. In children convulsions may occur. Weakness or loss of power of articulation is (according to Dr. Jennings) so constant as to be practically diagnostic of plague. The expression of activity gradually gives way to apathy from want of control over the facial muscles. The duration of the febrile stage would appear usually to be from two to five days, but sometimes it is much longer. The fall of temperature is generally described as sudden, and it may not rise again; but in some cases a recurrence of high temperature after three or four days is observed. In some fatal cases the rectal temperature



after death was found to be high. In cases which do well there is a gradual but irregular fall, and after fourteen days the temperature is often subnormal.

*Buboes* or inflammations of lymph-glands constitute the most important and characteristic feature of plague. They are rarely wanting, and are only in cases which are very rapidly fatal, and especially in the pneumonic form, though it is difficult to say in what proportion they are absent, since in the panic of an epidemic they may be overlooked. The term "bubonic plague" is therefore in the main accurate.

Buboes are in some instances the first symptoms to attract the attention of the patient, perhaps by a sudden lancinating pain. More usually they occur after the onset of fever, on the second, third, fourth, or even the fifth day of the disease. With the appearance of buboes there is often some abatement of the fever and general symptoms. The affected glands are generally extremely painful, but sometimes the enlargement is insidious, and only detected on examination. They may enlarge rapidly, more often gradually. Glands are usually affected in groups, but generally one is much larger than the rest. At first the glands are extremely hard, and in fatal or very severe cases may retain this character to the last; in other cases suppuration occurs, which is a favourable sign, and generally regarded as a favourable sign. It is often more prevalent during the decline of an epidemic. On the other hand, rapid softening, flattening, or even disappearance of a bubo during the height of the attack is sometimes observed, and is a sign of the worst omen, being speedily followed by death. It was so in London in 1665, and in later epidemics in Irak. Sometimes the skin over the bubo becomes gangrenous, forming a carbuncle. According to Mr Canth the great oedema scrofuli of the glands, converting the group into an elevated doughy mass, sometimes five or six inches in diameter. A bubo once formed usually lasts during the whole of the attack. In suppurative cases which recover the process may be prolonged for several days, or even for some weeks, and leave formidable scars, the diagnostic marks of a past attack of plague.

The size of a bubo does not generally exceed that of an almond or a walnut, but may attain that of an egg or small orange. Small and hard buboes are regarded as of more serious import than the large and soft. In the majority of cases (three fourths or more according to some observers) only a single prominent swelling occurs, but swollen glands are to be found in other regions if sought for. Generally about 75 per cent or more of the cases have buboes of some kind. With regard to *situational* observers agree that the inguinal group of glands is most frequently affected, such cases, according to Cabanis and Colvill (if with these be included those of the femoral triangle), making 40-50 per cent of the total number, but when the femoral glands have been distinguished from the inguinal, the former appeared to be most frequently attacked. Next in frequency of attack come the axillary glands—in 25 or 30 per cent of cases, and in a larger proportion of female patients, the cervical and submaxillary or other glands are only attacked occasionally. Some

Internal glands, especially the various abdominal groups, are always found inflamed on post-mortem examination. In four different sets of observations in India the proportion of inguinal (with femoral) glands affected varied from 63 to 70 per cent, of all cases with buboes. The axillary glands were affected in 15 to 20 per cent, the cervical in 5 to 15 per cent and in 3 to 5 per cent there was multiple gland affection. The mortality was generally highest in the cases of axillary buboes. It has been supposed that the great liability of the inguino-femoral glands was due to the bacillus entering the skin of the feet or legs in a barefooted population: but this is not confirmed by wider observation. The special liability of this glandular group is the same in every country where plague occurs, whether the inhabitants wear boots or not (Simpson). The situation of the bubo does not regularly correspond with the part where the infection enters the body, though sometimes such a relation is observed. Hence some pathologists hold that the buboes result from a general infection and the distribution of bacilli by the blood. Of secretory glands the parotid is sometimes, though rarely, inflamed.

*Carbuncles.*—Gangrenous patches of skin, or "carbuncles," though probably not the same as what are now called carbuncles proceeding from sebaceous glands, form another characteristic feature of plague. According to Camacho and Colvill, they occur, however, only in 2 or 2½ per cent of the cases. Red patches appear on the skin, and become indurated and sometimes vesicular, then necrosis occurs, which spreads till the patch may attain a width of some inches. They may occur on any part of the surface of the body, and have sometimes been attributed to direct introduction of the virus of plague into the skin. In recent Indian and Chinese epidemics this feature was distinctly less common than it would appear to have been in the older epidemics.

*Petechiae.*—Purpuric patches, due to ecchymoses, sometimes of small size (petechiae), sometimes larger, are often seen in severe cases. In the seventeenth century they were known as the "tokens," and regarded as markedly indicating the approach of death. Neither petechiae nor ecchymoses have formed important symptoms in the different outbreaks of the present pandemic, but they are occasionally well marked in severe cases before death (Simpson).

General pustular or vesicular eruptions have rarely been observed.

*Sweating* is an extremely variable symptom. In certain epidemics very profuse sweats have been observed, in others this feature has been entirely wanting.

*Hæmorrhage* from various organs is sometimes observed in severe cases, and is much more frequent in some epidemics than in others. *Pneumonia* is a common form of it, but pulmonary hæmorrhage, usually associated with congestion or pneumonia, is regarded as of specially serious import. It was observed in the first epidemic of the Black Death in Europe (1348), in the epidemic on the Volga in 1879, and on many other occasions. This is characteristic of the pneumonic form of the disease, and was at one time thought by Hirsch to be peculiar to Indian

plague. But though apparently commoner in the Indo-Chinese strain, it is by no means confined to that form of the disease.

Hæmatemesis is sometimes so noticeable as to have been called "black vomit"; and intestinal hæmorrhage produces black dejection. Urinary hæmorrhage and metrorrhagia may occur, and the cases are generally or always fatal. The hæmorrhagic form of plague, though not constituting a distinct type, may be compared to the hæmorrhagic forms of small-pox, scarlet fever, and so forth.

The remaining symptoms will be best considered in relation to the various systems of the body.

*Nervous System.*—The general features have been already described. There is profound poisoning, affecting especially the cerebrum, but with little disturbance of motor function, except occasional convulsions, and the contraction of tendons seen in the last stages of many febrile diseases. Paralysis does not appear in the descriptions except as one of the sequels of an attack. The violent or maniacal delirium of older records has been also noted in recent epidemics. Remarkable cases of this kind were observed in Bombay. Some patients shewed the tendency to leave their beds and rush wildly into the open air, or even attempted to travel to a distance, as has often been observed in typhus and small-pox. In some cases there was a tendency to homicidal or suicidal mania.

*Respiratory System.*—The respiration is accelerated in the febrile state in proportion to the fever, perhaps more so. In some epidemics marked symptoms of engorgement of the lungs and pneumonia with profuse hæmoptysis are described. These cases are now recognised as the pneumonic form if unaccompanied by buboes. But secondary broncho-pneumonia and bronchitis are not unfrequently met with in ordinary bubonic plague. These cases have in some instances given rise to an erroneous diagnosis of epidemic pneumonia. In Hong-Kong pulmonary symptoms were absent. These variations are perhaps partly connected with differences of climate and season.

*Digestive System.*—Beside the condition of the tongue already noticed, some cases give evidence of grave gastric disturbance, in the form of severe bilious vomiting; this is sometimes an early symptom, but it may occur at any stage. The bowels are constipated, as a rule, but profuse diarrhoea sometimes occurs, and has been regarded (Colvill, Cantlie) as a favourable symptom. The occurrence of gastro-intestinal hæmorrhage has already been noted.

*Blood and Circulation.*—The French physicians in Egypt in 1835-36, at a time when bleeding was customary, made some analyses, from which it appears that the blood coagulated imperfectly, and never formed a buffy coat. Its surface presented fatty globules, the serum was deeply coloured, and in some instances the reaction of free sulphuretted hydrogen was obtained. The water was in excess. These results would shew profound decomposition and destruction of red corpuscles. The late Dr. H. F. Müller in Bombay observed a dark colour and high venosity in

a drop of blood obtained by puncture when heart failure was beginning, but no colouring of the serum. Marked leucocytosis has been observed (15,000), and in single cases even 120,000, and 200,000 (Aoyama). The increase affected the polymorphonuclear leucocytes. Alterations in the red corpuscles are not constant. The bacillus is not detected in the blood till the disease is at its height, and is numerous in the later stages only. Cultivation is more successful than microscopical inspection for its detection. Albrecht and Ghon found it in 45 per cent of the cases; the German Commission in a smaller proportion. Cases with bacilli in the blood seldom recover. The *Circulatory* disturbances have been described. The spleen is generally enlarged.

The *Urinary System* presents nothing very notable. The urine is generally diminished, sometimes suppressed; but in the Hong Kong epidemic it was normal. Hematuria and albuminuria sometimes occur.

*Duration of Attack.*—Cases are sometimes fatal within a day, but in general the duration of fatal attacks is three to five days. Colvill, in Baghdad, found that nearly one fourth of his fatal cases died on the first day, about three-fifths within three days, and five-sixths within five, a very small number of such cases lived over a week. Hence if a patient lived as long as this, he was thought pretty certain to recover. On the other hand, cases in which suppuration of buboes occurs, and which recover, may be protracted to three weeks or a month. Dr. Simpson gives as the result of his experience that death may occur within one or two days or even less, but may be later, from the third to the seventh day, but usually occurs between the second and the sixth.

*Mortality.*—Plague is the most fatal of all known epidemic diseases affecting large numbers. At the beginning of an epidemic the mortality is often 80 to 90 per cent or more of those attacked, and this rate is maintained or increased at the height of the epidemic. During the epidemic on the Volga in 1879, in one group of villages visited by myself, every person attacked by plague had died. Towards the end of every epidemic recoveries predominate over deaths, so that the average mortality falls, but in some limited epidemics in Irak three-fourths of those attacked have died, and in others the mortality has risen to 90 per cent or more. In the larger epidemics of Baghdad in 1876, the proportion of deaths was officially stated as 55·7 per cent; and at Hillah in the same country it was given by Cabiadis at 52·6 per cent. In other epidemics the percentage of fatal cases has not been more than 40 per cent, and in Egypt in 1834-35 about one third. In India the general case mortality has been 70 to 85 per cent among natives. In Hong Kong 89 to 96 per cent of Chinese, but less among Indians (77 per cent) and Japanese (60 per cent) living there. In South Africa for the coloured population 56 per cent, in South America (Asuncion) 50 to 66 per cent (Simpson). The above statistics refer to native inhabitants. The mortality among Europeans was much less. In Hong Kong it was 31·6 per cent, in Bombay 30 to 40 per cent; in Cape Town 33·3 per cent.

Our Australian colonial populations have shewn a mortality of 31 or 32 per cent of the cases.

The total mortality has notoriously been in many instances very great both absolutely and in proportion to the population, though older accounts may have been exaggerated. The Black Death is calculated to have carried off one-third of the inhabitants of Europe, and in some countries more than one-half, but these estimates must be uncertain. In modern times it is said that the plague of 1830-31 killed 60,000 of the 150,000 inhabitants of Baghdad. The epidemic of 1876 in Irak is stated to have destroyed one-eighth of the whole population. In 1881 most of the villages affected lost a moiety or more of their inhabitants. As in such times a large part of the surviving population seeks safety in flight, it is easy to understand how villages may be entirely ruined and depopulated by the ravages of plague, as was the case also in our own country in the fourteenth century. The mortality in India has been noticed on p. 362.

**III. Pneumonic Form, or Primary Plague Pneumonia.**—This form has been observed at various times, as in the first epidemic of the Black Death in 1348, in the Pali Plague 1838, and other Indian epidemics, and at Vetlanka, Russia, 1878-79. Forbes gave a clinical description of cases in Pali 1838, of which the late Dr. H. F. Müller said that, apart from some details, there was nothing to add, nor anything to take away. Pneumonic plague was, however, first discriminated as a special form by Dr. L. F. Childe at Bombay in 1897, from cases most of which had been diagnosed during life as pneumonia, not plague. It should be remembered that bronchopneumonia of greater or less severity is a not infrequent complication in bubonic plague, and is distinguished as *secondary pneumonia*.

*Symptoms and Clinical Course.*—The attack begins usually with one violent rigor, or repeated shivers, but these may be wanting. There are no prodromal symptoms. Headache, giddiness, vomiting, variable in intensity, follow. There is no primary bubo. The facial expression is one of great anxiety and there is imperfect articulation as in the bubonic form. Pleuritic pain may be felt on the second, third, or fourth day; cough, with expectoration, and râles heard on auscultation may commence on the third, fourth, or fifth. The temperature is high, but does not differ specially from that in other forms of plague. The prominent symptoms are cough and blood-stained expectoration. Sometimes, but not always, marked hæmoptysis and excessive dyspnoea with a tendency to cyanosis. The respiration rate, according to Müller, was as a rule over fifty, sometimes rising to seventy-five. The auscultatory signs are those of lobular pneumonia. The dulness on percussion is not marked. The sputa have no characteristic appearance, but are found to contain bacilli in enormous numbers. These are also detected in the blood. Swelling of the spleen is very marked. Death occurs from failure of the heart. In the older accounts death is said to have occurred within two days. At Bombay about half the cases were fatal within five days, but



were prolonged to a week or more. The disease is almost invariably fatal.

Pneumonic plague is highly contagious and generally reproduces the same form: this was the case in a series of eighteen cases observed at Bombay. Sometimes by accidental inoculation the bubonic form results. In one case at Bombay a portion of sputum falling on the conjunctiva gave rise to ordinary bubonic plague.

Post mortem examination shews, besides the signs of scattered foci of pneumonia in the lungs, inflammation of the bronchial glands.

**IV. Septicæmic or Septic Form.**—This is an extremely virulent and rapidly fatal form of plague, in which, as in the pneumonic, buboes are absent, or not discovered during life. Some observers do not recognise it as a distinct form. It is distinguished by the large number of bacilli circulating in the blood and by clinical characters.

The attack begins, as in other forms, with rigors, headache, vomiting, and high fever. In some cases the temperature is below 100 F (Simpson). The implication of the nervous system is very marked. "Extreme nervous prostration, weakness, drowsiness, restlessness, hurried and panting respiration, small and full pulse, tympanites, delirium, picking of the bed clothes, stupor, and coma quickly follow." There may be bleeding from the nose, kidneys, and bowels. Death may occur on the first, second, or third day, with symptoms of collapse. If the patient survive longer buboes may appear. In fatality this comes near to the pneumonic form.

**Prognosis.** The most unfavourable symptoms are hæmorrhage, in whatever form, and petechial eruptions or "tokens", both affections are generally lethal prognostics. Profound affection of the nervous system is also an unfavourable sign, and so is abundance of bacilli in the blood. Suppuration of buboes is always of good omen. Sex and age appear to have little or no influence on the result. All observers agree that prognosis is generally very uncertain, and that cases apparently mild often terminate fatally.

**Diagnosis.**—Absolute diagnosis is best made, when practicable, by the detection of the bacillus in the tissues or fluids of buboes or other parts. But when this is not possible, there are other signs which may be sufficient for diagnostic purposes. No acute febrile disease presents the peculiar affection of the lymph glands. Nevertheless a casual lymphatic inflammation or an inflamed parotid gland may occur in rare cases of other diseases, especially in typhus, which was at one time thought to show in some cases a transition to plague. Modern observers, however, have found no difficulty in making the diagnosis, the longer duration of typhus ("the fourteen days' fever") and the collective symptoms making a well-marked distinction. Malignant forms of malaria have sometimes been confounded with plague, but the absence of intermissions, or even of definite remission of the fever, and the inefficacy of quinine, are obvious distinctions. The aspect or facies of a malarial patient is also very different. But if suspicion has not been aroused, mistakes in

diagnosis are frequently made; and at the beginning of an epidemic the disease has been often, not to say generally, unrecognised. The chief points to be attended to, apart from glandular enlargements, are—the sudden onset, the high temperature with dry skin; character of the tongue and injection of conjunctivæ; intense headache, insomnia, delirium, and sometimes vomiting; the peculiar facial expression above mentioned: peculiar manner, refusal to answer questions, and (as some say) disinclination of the patient to allow that he is ill.

**Treatment.**—The treatment of plague cannot be regarded as satisfactory, but the newer method of serum treatment is more promising than the merely symptomatic therapeutics formerly adopted. In old days opinions were divided as to the value of bleeding, but the balance of experience was decidedly against it. The violent sudorifics used in the seventeenth century appear to have been useless.

In modern times quinine has naturally been largely administered, but the general testimony is that it is quite useless. Antiseptics (such as carbolic acid, salicylic acid), antipyretics, and cardiac stimulants have all been tried with no better results; purging with calomel and magnesium was largely used in Hong-Kong, but with little benefit. In fact, nothing approaching to a specific or antidote in the way of drugs has ever been discovered. The general principles of treatment would seem to be, as in other asthenic fevers, to give the patient an abundant supply of fresh air, to avoid overcrowding, to use cold affusions or baths in the height of the fever, and to administer such cooling or other drinks as may promote his comfort. When the strength is failing, stimulants are of course indicated, but alcoholic stimulation appears to be of less value than in typhus. In the seventeenth century some good observers denounced the use of “strong waters” as positively pernicious. Hypodermic injections of strychnine have been largely employed, and with good effect. Digitalis and strophanthus are recommended to sustain the force of the heart. In a malady of such short duration the utility of abundant nutrition would appear to be of less importance than in more protracted illnesses. One of the most important factors in assisting the patient's recovery, as well as in preventing contagion, is abundant, or even superabundant ventilation, the good effects of which are well known in the treatment of typhus.

Major Thomson and Dr. Thomson, in their treatise on plague, lay great stress on keeping the patient prone till the temperature has been normal for at least four days. “Injudicious breach of this rule, by allowing patients to sit up, led to the death by syncope of twenty convalescents.”

The local treatment of the buboes has received much attention. The general result of experience is that energetic treatment by caustics, mercurial inunction, or early surgical interference, is painful and fruitless. In early stages soothing applications only, such as poultices, anodyne or ice-bags, should be used. When softening or suppuration occurs surgical treatment by incision and drainage is called for, but nothing



gated by too early incision (Simpson). There is no evidence of the value of thorough antiseptic surgical methods, but in the Hong Kong epidemic the injection into the glands of solutions of perchloride of mercury and carbolic acid seemed to be of temporary benefit.

J. F. P.

**Specific Prophylaxis and Cure.**—The basis of the attempts to immunise human beings against plague is the oft-repeated observation that recovery from an attack of the disease confers immunity, although the individuals continue to be exposed to infection. This observation has been utilised in the employment in pest hospitals of nurses and attendants who have had the disease (Netter). The immunity, however, is not absolute, as in many epidemics it has been noted that patients may succumb to a second attack of plague after successfully passing through a first. Thus, several cases were submitted to the Indian Plague Commission, in which two and even three attacks had occurred in the same person, the intervals between the attacks varying from eight days to twenty-six months.

The artificial establishment of immunity against plague may be brought about, as in certain other infective diseases, in two ways. (A) Active immunisation, by the inoculation of cultures of the plague bacillus or its products. (B) Passive immunisation, by the inoculation of the blood serum of animals which have undergone active immunisation. Some observers recommend a combination of these two methods for use in man.

**A. Active Immunisation.**—This has been practised in India on a very large scale, and we are in possession of a large number of facts dealing with this question. In general, the active immunising agents used in connexion with plague may be divided into four groups, viz. (1) the inoculation of cultures (broth or agar) which have been heated so as to destroy the vitality of the plague bacillus. This is the basis of the vaccines used by Haffkine and the German Plague Commission; (2) inoculation of products prepared directly from cultures of plague bacilli (Lüstring and Galeotti's vaccin); (3) inoculation of products derived from the bodies of animals recently inoculated with living plague cultures—e.g. Terni and Bandi's vaccin, Hueppe and Kikuchi's vaccin, Klein's prophylactic; (4) inoculation of living cultures attenuated spontaneously or artificially—e.g. Koller's vaccin.

As the active immunisation by killed cultures is the only one which has been applied to man on a large scale, it will be necessary to refer to it in detail. The immunising value of dead cultures of *Bacillus pestis* was first observed by Yersin, Calmette, and Borrel in the case of rabbits which were found to withstand doses of living virulent plague cultures, provided that they had previously been treated with agar cultures heated to 58° C. The experimental results gained by these investigators were then applied to man by Haffkine in his plague prophylactic. In the preparation of this agent broth-cultures inoculated

with plague bacilli are grown for one month, and after testing their purity, the bacilli are destroyed by heat at 65 to 70° C. As a further precaution a quantity of carbolic acid is usually added. From the first, great difficulty was experienced in adequately standardising the vaccin, so that the dose was more or less arbitrary, and varied in different samples between 5 and 20 c.c. With a vaccin prepared as above Haffkine first of all inoculated himself (10th January 1897), the resulting symptoms being severe pain, tenderness, fever, and considerable malaise. Almost immediately after this experiment large numbers of people in India availed themselves of the protection assumed to be afforded by the plague prophylactic, and the earliest results were strongly in its favour, for of 8142 persons inoculated in Bombay only eighteen developed plague. Before, however, dealing with the statistical data on which the true value of Haffkine's vaccin is based, it is necessary to consider the questions of its dosage, standardisation, and the results that have been determined experimentally in the case of animals. Even at the present time considerable doubt exists as to whether the immunising principle of Haffkine's vaccin is contained in the fluid part, in the sediment, or in both. Contrary to the opinion of Kolle, Liston, and others, Dr Klein (141) found that the fluid part of the vaccin is endowed with protective properties. In Captain Douglas's recent experiments with the filtrate from seven different vaccins, 52.5 per cent of the rats immunised with the filtrates survived lethal doses of living plague bacilli administered at the end of ten days. It would appear also that the degree of virulence of the plague culture is not a matter of great moment in the manufacture of the prophylactic, as Captain Douglas obtained a high degree of protection from vaccins prepared from cultures which were practically non-virulent. Haffkine judged the strength of his vaccin and the dose to be employed by the degree of opacity which it presented to the naked eye, or in its first inoculations by the equally unsatisfactory method of determining the dose necessary to produce a certain rise of temperature when injected into human beings. In his evidence before the Indian Commission, Captain Douglas shewed that the amount of sediment was sometimes seven times as much in some vaccins as in others. Even at the present time, however, the difficulty of standardisation has not been surmounted, and it would seem that the only feasible method is to inoculate comparative groups of human beings with varying doses, and to determine which dose leads to a maximum production of antibodies in the blood, or which dose leads to the greatest protection when the inoculated individuals are exposed to the natural risks of plague infection.

The effects of the inoculation of Haffkine's vaccin can only be described as severe. Three hours after inoculating himself with a dose of 1 c.c. of a six weeks old dead broth culture, Captain Douglas was seized with a rigor; considerable febrile disturbance lasted for several days, accompanied by great malaise and pain at the point of the inoculation. To what extent these unpleasant symptoms are a necessary part of a successful plague vaccination is not known.

*Results obtained in India by the use of Haffkine's Prophylactic.*—Although the methods of standardising the vaccin were crude, and although it was frequently contaminated by extraneous microbes, the Indian Plague Commission, after a searching inquiry into the whole question, reported favourably on Haffkine's method of active immunisation. The conclusions of the Indian Commission gave a considerable impetus to the practice of inoculation, and large numbers of people were inoculated when plague spread into the Punjab. Unfortunately a disaster occurred at Malkowal on November 1902, when nineteen people, inoculated from the same bottle of vaccin, were attacked with tetanus and all succumbed. This, combined with racial prejudices, has done a great deal to thwart the progress of plague vaccination. In reference to the value of the statistics, it was considered by the Commission that the following series of inoculations were the least fallacious, viz. those at the Byculla house of correction, at Umarmkhadi, Undhera, Bangalore, Bulsar, Lanauli, Kirki, Gadag, and Daman. In the subjoined table the total results have been worked out from data given by the Commission.

	No. of Cases Inoculated.	Cases of Plague.	Per cent of Plague Cases.	Deaths from Plague.	Per cent of Deaths from Plague.	Case-Mortality per cent.
Uninoculated . . .	11,272	469	4.16	348	3.08	74
Inoculated . . .	15,082	342	2.26	147	0.98	43

Taking all the facts into consideration, the Indian Plague Commission arrived at the following conclusions: (1) "Inoculation sensibly diminishes the incidence of plague attacks on the inoculated population, but the protection afforded against attacks is not absolute. (2) Inoculation diminishes the death-rate among the inoculated population. This is due not only to the fact that the rate-attack is diminished, but also to the fact that the fatality of the attack is diminished. (3) Inoculation does not appear to confer any great degree of protection within the first few days after the inoculation has been performed. (4) Inoculation confers a protection which certainly lasts for some considerable number of weeks. It is possible that the protection lasts for a number of months."

With a properly standardised and sterile vaccin, and with a dose accurately determined to be the optimal one, very much better results might be expected.

*Other Vaccins.*—The difficulties of standardising Haffkine's prophylactic, and also the severe effects induced by its inoculation, led the German Plague Commission to recommend the use of killed agar cultures. Experimentally a vaccin made in this way gives good protection, but it has not been extensively used on man. Lustig and Galeotti isolated

a nucleo-proteid immunising substance from plague cultures by digesting the bacilli with potash and then precipitating with dilute acetone. The precipitate is then dried and constitutes the vaccin. In the adult the dose is stated to be 2 to 3 mgr. This vaccin was employed to protect 600 people in San Nicola (La Plata), and no one contracted plague. Shiga recommended protection by a combined use of plague serum and heated agar cultures, this method being employed in forty-seven cases in Osaka and Kobe. Besredka made a vaccin by digesting the bacilli with saline solution and subsequently precipitating the bacillary bodies by a strong agglutinating serum.

Both the German and Austrian Plague Commissions point out that living cultures which had undergone attenuation might be used as vaccinating agents. In 1902 Kolle and Otto made a large number of experiments with an old living laboratory culture which had undergone attenuation, and reported very successful results concerning the immunisation of guinea-pigs. Thus, of thirty-four guinea-pigs inoculated with the attenuated culture, 76 per cent survived the introduction of virulent cultures at a subsequent date. Recently Kolle and Strong reported the results obtained by inoculating living attenuated cultures into human beings. The cultures were so attenuated that an entire agar culture would not kill a guinea-pig. The first injections were made out in the Philippines by Strong on prisoners under the sentence of death,  $\frac{1}{100}$  of a loopful of living bacilli being inoculated under the skin without appreciable effect. Later it was found that a whole loopful of culture could be inoculated without any severe reaction. Of four human beings inoculated in this way it was noted that the temperature begins to rise a few hours after inoculation, occasionally reaching 102°. By the third day the temperature falls; the local lesions are small. The degree of protection afforded by vaccinating human beings with living cultures has not yet been determined, but from similar experiments on monkeys and guinea-pigs it may be expected to be high. Naturally very great care would be necessary in recommending a method of this kind on a big scale in plague-stricken communities, as from unfavourable circumstances the virulence might increase and plague be introduced. As long ago as 1755, Wesspremi suggested the artificial inoculation of pest on the lines of variolisation, and in 1781 a Russian physician Samoilowitz, inoculated himself with plague pus: he passed through a mild attack of bubonic pest and became immune. He recommended the application to the unbroken skin of a pledget of lint saturated with bubonic pus. Other experimenters had, however, very unfavourable results. Thus Cerutti inoculated six persons, five of whom died of pest.

Terni and Bandi have prepared a vaccin from the peritoneal exudate of animals inoculated with living virulent pest cultures. Immediately after the animals succumb the peritoneal exudate is collected and incubated at 37° C. for twelve hours. The vitality of the contained bacilli is destroyed by heat at 52° C., and the fluid is then diluted

with water containing carbolic acid. This vaccine is said to have good immunising powers. Hueppe and Kikuchi have recently described a somewhat similar method depending on the presence of aggressins obtained by the method of Bail. On the same principle is the new plague prophylactic advocated by Dr. Klein (142). This is prepared from the necrotic plague nodules in the buboes and spleen by drying over sulphuric acid at 46 to 47 C until complete sterility is obtained. 10 to 15 mgr. of the dry powder suffice to protect rats against virulent plague bacilli.

**B. Passive Immunisation.—Anti-plague Serum.**—Following the lines laid down by Behring and Kitasato for diphtheria and tetanus, Yersin, Cuminette, and Borrel immunised horses with plague cultures, and asserted that after a time the serum acquires antidotal properties preventing or curing a pest infection in animals. In general, two types of anti-plague serum may be recognised, viz. one derived from the inoculation with cultures of plague bacilli (Paris serum, Berne serum, Lister Institute serum, Brazil's serum), and one derived from the inoculation of animals with nucleoproteids produced from cultures (Lustig's serum). In the former of these horses are treated first with killed then with living cultures in doses gradually increasing till quantities as large as 100 c.c. can be tolerated without danger. At first the inoculations are made subcutaneously but afterwards intravenously. The horses are bled about three to four weeks after complete recovery has been established. Apart from determining whether the serum is toxic, accurate standardisation does not appear to be carried out, the dose recommended for man being entirely empirical. Since small doses failed, larger doses have been tried, and in India, in accordance with Roux's recommendation, an initial dose of 100 c.c. was used. Quantities up to 235 c.c. (Walton and Douglas), and in one case 700 c.c. (West), were given but failed to prevent a fatal issue. Apart from the ordinary effects witnessed on injecting alien serum, no serious complications occurred. In regard to the experimental evidence of the protection afforded by plague serum, Koch, v. Behring, Pfeiffer, Kolle, and Martini found that it could prevent a fatal issue, provided it were inoculated first. Whereas, if living virulent plague bacilli were injected at the same time as the serum, the latter was practically valueless, and still less so if the plague culture were injected first. As has been observed in man, the serum, however, appears to prolong life.

**Results in Man.**—In India Yersin obtained relatively favourable results, as did other observers, when selected cases only were treated. Wherever cases have not been selected and a series of strict controls have been taken, practically no advantage has been seen in the serum group. Thus in the cases treated by Captains Douglas and Walton the following were the results—

1. Bangalore.

	Cases.	Deaths.	Case-Mortality.
Treated with serum . . .	49	31	63·2
Treated without serum . . .	54	29	53·7

2. In Bombay every second case was treated with serum, the others serving as controls. In this series the cases were strictly comparable both as regards severity of type and period of disease.

	Cases.	Deaths.	Case-Mortality.
Treated with serum . . .	28	24	85·71
Treated without serum . . .	28	23	82·14

In the entire series of cases (treated with Paris serum) in which reliable controls existed, Captains Walton and Douglas had the following experience :—

	Cases.	Deaths.	Recoveries.	Case-Mortality.
Treated with serum . . .	226	168	58	74·83
Treated without serum . . .	231	163	68	70·56

The exhaustive analysis of all the available data compelled the Indian Plague Commission to the conclusion that the “method of serum-therapy as applied to plague has not been crowned with a therapeutic success in any way comparable to that obtained by the application of the serum method to the treatment of diphtheria.” Still more recently Colonel Bannerman (118) has analysed the results obtained in India up to May 1904, and has also come to the conclusion that anti-pest serum is much less efficacious than diphtheria antitoxin. The following table, taken from Colonel Bannerman’s paper, refers only to cases “in which the conditions of trial were reasonably accurate, and in which a series of control patients strictly comparable with those treated with serum was available.”

	Serum Cases.				Control Cases.			
	No.	Deaths.	Recov- eries.	Case- Mortality per cent.	No.	Deaths.	Recov- eries.	Case- Mortality per cent.
rsin serum by In- lague Commission (Dore)	49	31	18	63·26	54	29	25	53·7
rsin serum by In- lague Commission (May)	28	23	5	82·14	28	24	4	85·7
rsin serum by n Commission	50	40	10	80·0	50	40	10	80·0
rsin serum by Dr. 1902	31	29	2	93·54	31	29	2	93·54
rsin serum by Dr. Bombay)	68	45	23	66·17	68	41	27	60·29
ated with Roux- serum	226	168	58	74·33	231	163	68	70·56
serum (Dr. Turk- 900)	66	54	12	81·81	66	48	18	72·72
serum (Dr. Mayr,	31	31	...	100·0	31	29	2	93·54
serum (Poona,	27	21	6	77·7	28	20	8	71·42
serum (3rd series, y)	484	330	154	68·18	484	385	99	79·54
ated with Lustig's	608	436	172	71·71	609	482	127	79·14
serum . . . . .	110	89	21	80·90	110	90	20	81·81
serum (Maratha tal)	50	41	9	82·0	50	45	5	90·0
serum (Modikhana al)	20	17	3	85·0	20	15	5	75·0
ted with Brazil's	70	58	12	82·85	70	60	10	85·71

the serum is unable to influence the case-mortality in any



marked degree it would appear that life is frequently prolonged by its use, as is seen in the following table also taken from Col. Bannerman (118).

Kind of Serum Used.	Average Number of Days in Hospital in Fatal Cases in		Advantage in Favour of Serum Cases.	
	Serum Cases.	Control Cases.		
Roux . . . . .	7.57	4.19	3.38	
Lustig . . . . .	3.89	2.76	1.13	
Terni . . . . .	3.27	2.93	0.34	
Brazil {	Maratha Hospital . . . . .	2.56	2.25	0.31
	Modikhana Hospital . . . . .	2.06	4.61	- 2.55

It would also appear probable that intravenous are more beneficial than subcutaneous injections of the serum, as the absorption by the latter route is much slower.

	Serum Cases.			Control Cases.		
	No.	Deaths.	Case-Mortality per cent.	No.	Deaths.	Case-Mortality per cent.
Subcutaneous injection only . . . . .	43	29	67.4	43	28	65.1
Subcutaneous injection followed by intravenous injection.	12	8	66.6	12	6	50.0
Primary intravenous injection followed by similar injections or in some few cases by subcutaneous medication.	13	8	61.5	13	7	53.8
	68	45	66.2	68	41	60.3

*Mode of Action of Anti plague Serum.*—Considerable doubt exists whether anti plague serum possesses bactericidal properties or not. According to Kolle, slightly virulent plague bacilli are dissolved by the serum *in vivo*. Sir A. E. Wright and Captain Windsor were unable to demonstrate any bacteriolytic action in normal serum *in vitro*. Markl attributes the action of plague serum mainly to phagocytosis, and in conformity with this observation Captain Douglas found that after inoculation of Haffkine's vaccine the opsonic index of the serum rose to three times the normal strength, but fell away after the ninth day. Markl also attributes antitoxic properties to anti plague serum. Under the influence of injections of plague culture

*proteolysins* are developed in the serum, and if plague serum be added to titrates from plague cultures, an abundant development of *proteolysins* can also be seen.

W. B.  
S. R. D.

### SPECIFIC PROPHYLAXIS AND TREATMENT

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W. B.

**Prophylaxis and Prevention of Plague.**—The measures comprised under this head have for their object (a) to prevent the transmission of plague from one place to another; (b) to prevent the spread of plague, when the disease, or its germs, have been introduced into any place; (c) to remove or modify local conditions which make the place a favourable soil for the growth of either endemic or imported plague.

(a) Regulations intended to secure the first of these objects have been known and practised for centuries. Since it was long ago observed that sick persons or contaminated objects might carry the infection, the rough method of total exclusion was adopted to prevent transmission of the disease. But when it was found that this practice involved complete stoppage of trade and intercourse, and was, moreover, not always effectual, the attempt was made to permit intercourse under such conditions that the infection should be kept out. The measures founded on this principle constitute what is strictly called *quarantine*. The system thus called was framed by the Venetians about the year 1485, with a reference to sea traffic, especially to their trade with the Levant; and was the model for all the similar regulations which governed European trade for centuries; being applied, with necessary modifications, to land traffic also. It remains a marvellous product of Italian ingenuity; such faults as it had being due to imperfect knowledge, or to mistaken principles. The system consisted in careful examination of all ships coming from infected or suspected countries; the detention of those to which any suspicion attached, and the removal from them of all persons and merchandise to

strictly isolated buildings called Lazarettoes, where they were detained for forty days. During this time the passengers were carefully watched for the appearance of any symptoms of illness, while all merchandise, personal effects, and clothing were submitted to a minute process of disinfection by exposure to air and sunlight. If any case of plague occurred, the period of forty days had to be begun afresh. The system is now obsolete, and need not be minutely described; but there can be little doubt that while it was in force it was, though not always successful, even in Venice, largely efficacious in preventing the introduction of plague from the Levant into European ports. At Marseilles, for instance, there were several instances of plague being arrested in the quarantine station, and not spreading into the town: though on the memorable occasion of 1720 these precautions failed, and plague forced the barriers, producing a celebrated epidemic. In other Mediterranean ports, immunity was secured for many years. The old quarantine system was an international arrangement secured by treaties, and was not formally abolished till 1897. In England it cannot be said that any quarantine system was ever regularly enforced; the policy in regard to plague oscillating between extreme laxity and the temporary enforcement of total stoppage of traffic. A very rigorous system recommended by Mead in 1720 never had to be put into practice. The first Act of Parliament establishing a general quarantine system was the outcome of a Parliamentary Commission in 1819, at which time it was hardly needed. The system was finally abolished in 1897 by the repeal of that Act.

To prevent the spread of plague on land the old custom, which lasted up to the last few years, was to surround the infected town or district with a military *cordon*, which persons were prohibited to cross under pain of death. In the eighteenth century some people were actually shot for breaches of these rules.

*International Agreements as to the Prophylaxis of Plague.*—The regulations now in force are based upon the decisions of the International Sanitary Conventions, held at Venice in 1897 and at Paris in 1903, regarding cholera and plague. The later Convention added certain regulations as to the destruction of rats on infected or suspected ships. The chief provisions agreed to at these Conventions are:—(1) That every Government must immediately notify to the other Governments the first appearance of recognised cases of plague in its territory; and, beside other details, the presence of that disease or of unusual mortality among rats and mice. (2) When several non-imported cases of plague have occurred in a certain place, that local area shall be declared infected; and the Government of that country shall take measures to prevent the spread of the epidemic. Other Governments may adopt any measures they think proper with regard to arrivals from an infected area or country, but must immediately make these arrangements public. (3) To prevent exportation of plague from infected ports there must be

medical inspection of the crew and passengers of outward-bound ships, detention of persons with suspicious symptoms, and disinfection of suspected articles. (4) To prevent importation of plague by ships from infected ports, special measures are authorised. After medical inspection such ships are declared *healthy*, if they have left the infected port for ten days or more and plague has not appeared. If cases of plague have occurred on board, but not within twelve days, such ships are declared *suspected*. If plague has occurred on board within twelve days, the ship is *infected*. These are differently treated. *Healthy* ships are subjected to no restrictions; but the crew and passengers are placed under surveillance for ten days from the date of leaving the infected port; that is, the names and destinations are recorded, and information is given to the Health Authorities of the places to which they are going. In *suspected* ships those parts of the ship exposed to infection must be disinfected, and the persons are kept under surveillance for five days from the date of arrival. Destruction of rats on board is recommended. In the case of *infected* ships, the sick are at once disembarked and isolated; other persons are isolated for five days, and kept under surveillance for ten days, at the discretion of the authorities. Those parts of the ship which have been infected by plague-patients must be disinfected, and baggage and personal effects also, at the discretion of the authorities. Rats on board must be destroyed as quickly as possible; and, in any case, within forty-eight hours. Even a healthy ship in which rats affected with plague have been found, or where there has been an unusual mortality of them, is subject to similar rules for destruction of rats, disinfection, and surveillance of persons.

*Land Quarantine.*—The regulations for quarantine on land frontiers are much simplified. The old system of "Sanitary Cordons," intended to prohibit all communication with an infected place, is now recognised as useless, and as having special dangers of its own. But there is to be medical inspection at the frontier of all travellers, with detention of sick or suspicious cases, and disinfection of personal effects belonging to such persons. Merchandise, in general, is not subject to detention, but exclusion or compulsory disinfection may be applied to certain articles of personal use, such as rugs, clothing, bedding; and to raw hides, animal refuse, hair, and the like. Postal traffic is not interfered with. Special regulations were made by the Paris Convention of 1903 for traffic through the Red Sea and the Suez Canal, and for pilgrimages to Mecca which need not be considered here.

*Preventive Measures against Plague in the United Kingdom.*—The regulations now in force, under the authority of the Local Government Board, against the introduction of plague are based upon the decisions of the International Sanitary Conventions, and were summarised as follows, by the late Sir Richard Thorne<sup>1</sup>:—(1) Medical examination

<sup>1</sup> "Reports and Papers on Bubonic Plague, issued by the Local Government Board, 1902." p. 34. The complete regulations may be found in the same volume.

persons on board ships arriving from infected or suspected ports ;  
 Removal to an isolation hospital of any person suffering from plague, suspected plague ; (3) Disinfection of articles believed to have had opportunity of becoming infected ; (4) Disinfection of those parts of the vessel occupied by the case of plague, or suspected plague ; (5) The taking of names and addresses of all persons, including the crew, on board ships where plague, or suspected plague, has occurred ; such persons being at liberty to proceed to their destinations ; (6) Transmission of these names and addresses to the sanitary authorities of the respective districts concerned, with the view that these newly arrived persons be kept under the supervision of the Medical Officer of Health for ten days. The enforcement of these precautions is directed by several memoranda issued by the Board. A supply of Haffkine's prophylactic is kept in readiness by the Board, to be supplied to any Medical Officer of Health who may require it. Arrangements have been made for testing by a bacteriological expert, appointed by the Board, the diagnosis of any plague cases that may be reported.

A special memorandum refers to *Ship-borne Rats and Plague*, of which the following are the chief heads:—(1) On the arrival of a vessel whereon plague, or suspected plague, has occurred, methods should be taken to destroy the rats on board the vessel. Until this has been done, endeavour should be made to prevent rats leaving the ship by mooring the vessel in an isolated position, and by placing guards on cables and hawsers used for mooring purposes. (2) In the case of vessels arriving from infected places, even if no plague, or suspected plague, have occurred, strict inquiry should be made as to mortality or sickness among rats during the voyage. The body of a sick rat should be obtained, in order to ascertain, by bacteriological examination, the nature of the malady affecting them. (3) Exceptional sickness or mortality on board of any vessel arriving in the district, from whatever port, should be viewed with suspicion. (4) Rats, when destroyed, should not be handled, but cremated. (5) In the event of the ship-rats being found to be infected with plague, all parts of the vessel frequented by those animals should be disinfected. (6) The authorities of seaport towns invaded by plague should endeavour to secure the destruction of all rats in the town, and to prevent their making their way on board vessels lying in the port (same Report, p. 54). These measures, which are evidently of the highest possible importance, appear in several instances to have prevented plague from becoming established in our seaport towns.

(b) **Prevention of the Spread of Plague in an Infected Locality.**—

When plague has once appeared in any inhabited place, measures are required to limit its spread, to prevent other persons from becoming infected, and to destroy, as far as possible, the active bacilli present, whether these are attached to the objects surrounding the sick, or in lower animals, especially rats. Formerly attempts were made to isolate the infection by shutting up the houses in which cases of plague occurred till all the inmates had either died or recovered. This was notoriously



the method adopted in the old London epidemics, including the great plague of 1665. These measures were not only cruel, as involving the almost certain infection of most of the inmates in the affected house, but dangerous, as such a house was, by concentration, converted into a more virulent focus of plague than it was originally.

The measures now adopted, which were also recommended by the more enlightened sanitary authorities even in old times, aim at isolation of the disease by evacuation of the house, the inmates being conveyed, if already infected, to a hospital, or, if unaffected, to an observation hospital. The rules now laid down by the Local Government Board in this country require:—(1) Immediate notification, enforced under penalty, to the Medical Officer of Health, and by him to the Central Board, of every recognised (or suspected) case of plague. (2) Prompt scientific diagnosis by bacteriological testing of material from such cases. To assist in the identification, arrangements are made by which such material may be sent by the Medical Officer of Health to the Central Authority for examination by experts. (3) The measures to be taken to prevent the spread of plague are, generally speaking, those available against the more ordinary epidemic diseases. "These include prompt removal of the sick persons to hospital and their isolation therein; the destruction or thorough disinfection of all infected articles, with the effectual disinfection also of the invaded dwelling-place; the keeping under observation during ten days, after detection of each plague case, of all persons who have been in contact with the patient, and house-to-house visitation for the discovery of unreported or suspicious cases; the abatement as speedily as possible of all insanitary conditions in the locality which may tend to the spread of the disease; and, in the case of death, the prompt disposal of the corpse, with all due precautions against its becoming a source of infection." . . . "An essential measure of precaution, in view of the observed relation between plague in rats and plague in the human subject, will be the prompt destruction of all rats in districts threatened or invaded by plague, care being taken that their carcasses are collected and burnt without being unduly handled" (94).

For the protection against infection of doctors, nurses, and others in attendance on the sick, or otherwise exposed to infection, the Board recommends the use of Haffkine's plague prophylactic, and is prepared to issue this material to the Medical Officers of Health of districts actually invaded by plague.

For the disinfection of contaminated objects, and for floors, the Board recommends the solution of perchloride of mercury as generally used (common sublimate, half an ounce; hydrochloric acid, one fluid ounce, with five grains of aniline blue in three gallons of water), or 1 per cent solution of chlorinated lime, or 1 in 50 of formalin. For disinfecting the interiors of rooms chlorine gas is preferred to sulphuric acid; but spraying of a liquid disinfectant (as above) on the walls and floors is more efficacious. In a later report (1904) the Board gives



results of examination by Dr. Haldane of the Clayton method for disinfecting ships and killing rats on board ship. This method is also applied to the disinfection of houses. It consists essentially in the combustion of sulphur at a very high temperature, producing not only sulphurous acid, but sulphuric anhydride and other sulphur products. This process has been carefully tested by Dr. Simpson, Dr. Hewlett, and others, and found to be the most satisfactory and efficient method for the purposes mentioned above (Simpson, p. 359, 391, etc.).

The regulations summarised above agree in the main with those carried out in all countries where plague has appeared, and in some places, as in Glasgow, with conspicuous success: but modifications are necessarily required by local circumstances. In the Indian cities popular opposition made it impossible to carry out such measures thoroughly.

In the Indian villages and small communities, a complete evacuation, with the removal of the population to temporary camps while their dwellings were being disinfected, was found to be very efficacious in checking epidemics, and was successfully carried out in the villages of the Punjab, by Captain James. Similar measures had, indeed, been adopted by the inhabitants of the Himalayan villages of their own accord. In Cape Town some plague-infected areas were completely cleared of their native population, who were provided with temporary dwellings in another quarter, and thus the plague was completely stamped out among the native population (Simpson).

For the destruction of rats, besides ordinary methods, the introduction by Danysz of a bacillus pathogenetic to them has been widely used for their destruction. In some places this method, of which the details cannot here be given, has been very efficacious, in other places much less so. Success appears to depend upon measures adapted to maintain the virulence of the cultures. It has been applied either by inoculating the number of rats, who are then set free to infect their brethren, or by distributing articles of food impregnated with the virus.

In the disinfection of contaminated objects, it has been shewn that exposure to abundant fresh air and sunlight are important adjuncts to all antiseptic treatment and may indeed be efficacious without chemical aids, though requiring a much longer time.

All measures adopted to prevent the spread of plague are based upon the supposition that the disease is directly or indirectly communicable from the sick to the healthy, and though it has been shewn that the contagiousness, in the ordinary sense, of plague is very limited, it is better to proceed on the supposition that it may be thus conveyed. The difficulties raised by adopting this hypothesis are less important than the possible dangers of neglecting the precautions thus suggested.

There may be some doubt as to whether what are called ordinary sanitary precautions—cleanliness, attention to drainage, prevention of overcrowding in dwellings, etc.—have any great influence in limiting the spread of plague; but there can be no doubt that the neglect of these renders any inhabited place a favourable soil for the growth of the germs

of plague; and that in places which exhibit some approach to "sanitary perfection" the disease is far less likely to establish itself.

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## MALTA FEVER

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**SYNONYMS:** *Mediterranean fever; Gastric remittent and Bilious remittent fever; Mediterranean gastric remittent fever; La febbre gastro-biliosa; Fasco-malarial fever; Intermittent typhoid; Adeno-typhoid; Febris complicata; Febris sudoralis; Typho-malarial fever; Pythogenic septicæmia; Rock fever; Neapolitan fever; Danubian fever.*

**Short Description.**—An endemic fever of long duration (usually lasting from a few weeks to many months), accompanied by profuse perspiration and constipation, and often followed by pains of a rheumatic or neuralgic character, with swelling of the joints, orchitis, and tenderness and enlargement of the spleen. The disease is further characterised by a small mortality, tedious convalescence, a constant liability to relapses, and well-marked anæmia. The term "Undulant" fever was suggested by Hughes (11), but as Col. Bruce has shewn these undulations are merely recrudescences or relapses of the fever, which may occur, and often do, in enteric and other fevers.

**History.**—In the *Epidemics* of Hippocrates there are passages which, making allowance for the differences between the modes of thought and expression of his day and those of our time, might almost pass for a brief description of the disease.

The earliest mention of this fever is found in the reports of the medical officers of the navy and army in the early part of the last century. That it undoubtedly existed not only in Malta, but also in other parts of the Mediterranean, is very clear from these reports. Burnett, writing on the fevers of the Mediterranean in 1816, describ

this disease as being one of a severe remittent malarial character. It was equally prevalent among the British occupants and the native population, but in both possibly somewhat modified by the food and insanitary conditions existing at that date. That it was the same fever as we are now discussing is evident from the statements, "Though fevers are more common than in England, they occasion less mortality than in the United Kingdom" and again, "Rheumatism was common, and often extremely intractable."

In the few published writings of the older medical officers of the navy and army it does not appear that the primary fever of this disease was distinguished from the malarial remittent or continued fevers. It was not till after the Crimean war that the distinction began to be made. During the years 1904-5-6 important investigations have been undertaken by a Committee appointed by the Royal Society, at the request of the Colonial Office, Admiralty, and War Office (16).

**Geographical Distribution.**—The island of Malta, from which this fever takes its name, is built up of sedimentary rocks, which have been divided into upper and lower limestones and various intermediate beds of sandstone, traversed by innumerable fissures. It is but scantily covered by soil. The surface presents the appearance of an inclined plane, sloping gradually to the south-west. The island contains neither river nor lake, and from its geological structure and the absorbent nature of the soil has little marshy or swampy ground. There is no exuberant vegetation, brushwood or forest: the verdure is scanty, and the greater part of the surface presents nothing to the view but the arid rock. The most prevalent winds are from the south-east, south, and north-west. That from the south-east, termed the *sirocco*, is common, and prevails principally during the autumnal months. The annual mean temperature is 68° F.: in the hottest month (July or August) it is 81° F.; in the coldest month (January), 55° F., the extreme yearly range (from highest to lowest temperature in the shade) is 56° F., namely, from 96° F. in July to 40° F. in January; the mean yearly range is about 48° F. The greater part of the rainfall, which is about twenty-four inches, falls in November, December, and January. During the summer the island is almost barren.

That the fever is not confined to Malta there is now ample proof. It has long been recognised as identical with the "rock fever" of Gibraltar, which view Donaldson (15) also confirms. Veale (15), who has seen many cases, believes that the fevers of Malta, Gibraltar, and Cyprus are all one and the same disease. In Italy it has been described as occurring at Naples, Benevento, and Civita Nova del Sarno. Tomaselli has seen a large number of cases in Catania in Sicily. In Constantinople, according to Patterson, this fever is common, and is known under the vague term "country fever." Capetanakis states that this fever tends to become frequent in the town of Candia, and is known by various names, such as "Italian fever," "Neapolitan fever," and so on. Apparently it was unknown there a few years ago (Bruce). As the result of three



years' careful study of this disease, Milnes is convinced that it is prevalent in all parts of the shores of the Mediterranean and Red Sea ; a case of fever at Sawaken or Massowah will not present features very different from those of a case at Malta or Naples. Oliver has seen and treated cases of fever contracted on the banks of the Danube which were neither pure malaria nor enteric fever. The cases were characterised by long duration, small mortality, and frequent relapses. Bill has shewn conclusively that Malta fever is endemic in certain parts of the Orange River Colony, and Major Lamb has isolated the *M. melitensis* from the spleens of a number of persons suspected to be suffering from Malta fever in the Punjab. It has also been reported from China, Fiji Islands, North America, West Indies, and South America. From this it is clear that this fever is not limited to any one place, but appears to diffuse itself over a wide area within the subtropical region. In its secondary stage, in persons who have contracted the disease in its endemic home, it may be seen in this country ; a case has, however, been reported as occurring in this country, contracted either at Plymouth or London, but no definite source of infection could be traced. It has never spread in this climate.

Like other diseases belonging to the tropical and subtropical zone, it is most frequently found near the shores of the sea-coast and on the banks of large rivers ; inland places being comparatively free from its attack. The smallest number of cases of the fever occurs in the cold months. The fever curve begins to rise in May, and reaches its highest point in July, August, and September. Although there is a great increase in the prevalence of Malta fever during the hot months, many cases also occur in winter.

**Etiology.**—Until the appearance in 1887 of Col. Bruce's (2) classical and scientific accounts of the fever, nothing definite was known as to its causation. From the accessible data available from statistics and records of the Army Medical Department (15) during the last century, and from the prevalence of its attacks during certain periods of the year, it was early apparent that its presence in Malta and Gibraltar was connected with faecal and organic matter from human sources. The earlier writers were of opinion that the poison might be diffused in the air, and that it entered the human system by way of the respiratory passages. Tomassini therefore alleged that it is a fever of miasmatic origin ; otherwise, he says, he was unable to account for its rapid diffusion on a large scale. In Naples this fever is said to frequent the low-lying parts of the town, and those localities especially where the sewers are discharged. Sewers and sewage works, where these have been undertaken, as in Valetta and Naples, appear to have had little influence in diminishing the attacks. Indeed these channels are so frequently pervious, and allow the faecal matter to soak into the pores of the soil, that they virtually become elongated cesspools.

The *Micrococcus melitensis* has not been found outside the bodies of warm-blooded animals, except under artificial conditions. In post-mortem



examinations Capt. Kennedy found it in the spleen, liver, kidneys, lymphatic glands, salivary glands, blood, and bile, but not in the intestines. He thinks the examination of the lymphatic glands the most important, as they are often the only organs which contain it. The members of the Committee (16) already referred to carefully examined into the various channels by which the micro-organism might be supposed to leave the body, and could not find the organism in the expired air, the saliva, sweat, or scrapings of the skin: the fæces were examined by Major Horrocks with a negative result. The urine seems to be one of the main channels by which the micrococcus leaves the body. Major Horrocks has isolated the *M. melitensis* thirty-nine times, and from the urine of thirteen different patients. He did not find it earlier than the fifteenth day or later than the eighty-second day of the disease. Capt. Kennedy examined sixty-one cases and isolated it from the urine in thirty-three. The earliest day he recovered it was the twenty-first and the latest the two hundredth and forty-ninth. These observations shew that the micrococcus is excreted in the urine of Malta fever cases from about the fifteenth day of the disease until after convalescence is established. The number of micrococci present, except in rare occasions, is small. Milk is an important channel by which the micrococcus leaves the body. Major Horrocks has clearly shewn that the milk of goats and cows contains the microbe, and there is every reason to suppose that human milk is no exception to this rule. The presence of micrococci in the blood has also been proved. It has been found by Dr. Gilmour in 82 per cent, and Dr. Zammit in 54 per cent of the cases examined. The channels by which the micrococcus gains entrance to the body have been very carefully investigated by the Commission. The weight of evidence is against its being spread by actual contact. It is very doubtful whether it can be conveyed by dust; ordinary dust contains few micrococci, and up to the present there is no proof that dust, as it occurs under natural conditions, ever conveys the disease. Infected water plays no part in the dissemination of the disease. "No connexion has ever been demonstrated between any particular branch of the public water-supply, nor any particular well or tank, and an outbreak of Mediterranean fever, though such connexion has been shewn with outbreaks of enteric fever in Malta" (Johnstone). The use of ice and aerated waters (which latter is carried on under Government supervision) has also been inquired into, but no connexion has ever been traced between these and Malta fever. There is no evidence, and no suspicion ever seems to have been excited, that aerated waters or ice was a cause. Milk is probably the most important medium in conveying the micrococcus from animals to man. The Commission found that about 50 per cent of the goats in Malta responded to the agglutination test, and that 10 per cent excrete the *M. melitensis* in their milk. This excretion may continue for three months without any symptoms of the disease in the goat or change in the appearance of the milk. It was also shewn that monkeys fed on infected milk contracted the disease, and there can be little doubt that this also occurs in man.

Whether the disease is propagated by the bites of biting insects, such as mosquitoes, fleas, is still undecided. Both Major Horrocks and Capt. Kennedy believe it to be extremely probable that human beings are infected by the bites of infected mosquitoes, and Dr. Zammit states that he infected a monkey by allowing mosquitoes (*Stegomyia fasciata*), that had previously fed on a Malta fever patient, to bite it.

As regards its remoter causes Malta fever differs somewhat from enteric fever. In the latter disease all observers agree that the predisposition is greater in childhood and early adult life; especially between the ages of twenty and twenty-five. On the other hand, although Malta fever is found in the young and in adults, men up to thirty-five years of age seem to suffer in the same proportion as those whose ages are between twenty and twenty-five. Tomaselli is of opinion that the greatest number of cases occurs between six years and thirty years of age; a smaller number between the ages of two and six, and of thirty to fifty; and very few above fifty. Sex appears to have little influence, but the disease is perhaps more common among men than women.

It would seem likely that intemperance, by diminishing the power of resistance in the individual, would increase the liability to contract Malta fever, but there is no proof that it does so. Few patients admitted to the military hospitals can be classed as intemperate, and none are broken down by this cause. There is no evidence that grief, fear, or other emotion enters into the causation, and the same may be said of bodily fatigue and overcrowding.

Formerly this fever was thought not to be contagious, but recent experiments on monkeys indicate that Malta fever may be conveyed from the sick to the healthy by intimate contact. Col. Davies writes: "Having reviewed the influence of water, food, and air with, on the whole, a negative result, the condition that appears to be most probably effective in the causation of hospital cases is the presence in the wards of a large quantity of disease-producing material in the bodies of the patients themselves." Transmission by direct contagion is not theoretically probable; by indirect contagion through clothing soiled with excretal discharges it is not improbable in the nature of the case, although there is no proof of this mode of spread. In regard to the transmission by fomites, Major Horrock's experiments shew that the *M. melitensis* could be recovered from khaki cotton, khaki serge, and blankets up to the eightieth day, and Dr. Shaw recovered it from blue serge on the seventy-eighth day. These experiments indicate that this form of dissemination is of practical importance, and that the necessity for the thorough disinfection of the clothing is obvious.

That Malta fever occurs in an epidemic form there can be no question. Marston (15) states that it alternates with enteric fever; and that when the latter disease is prevalent Malta fever is in abeyance. Col. Bruce has noticed the same alternation, and Tomaselli regards the fevers which occurred in Catania in 1872 and 1878 as different epidemics.

We find other characters which mark this fever as distinct from enteric. In enteric fever it is well recognised that the largest number of cases do not occur at the period of greatest heat, but usually from six weeks to two months afterwards; and the minimum is not reached until about the same length of time after that of the most intense cold. On the other hand, the season of the greatest prevalence of Malta fever is July and August, and the smallest number of attacks is in December—the two former being the hottest months, and the latter having a mean temperature considerably above the minimum.

**Bacteriology.**—Malta fever is due to the introduction into the system of the *Micromoccus melitensis*, first described by Col Bruce (2) in 1887. The following is mainly taken from his description. The coccus or coccobacillus is about  $0.33 \mu$  in diameter, and usually occurs singly or in pairs but where grown in broth it appears in short chains. In broth cultivations after about ten days' incubation it is not uncommon to find chains of ten to fourteen members; these are very readily broken up, so that attempts to make permanent specimens are not invariably successful. A bacillary form also occurs in cultures which have been grown at ordinary temperatures ( $18^{\circ} \text{C.}$  to  $20^{\circ} \text{C.}$ ). Agar cultures which have been started for a few weeks (e.g. four) at room temperature often consist almost entirely of bacilli; the same is true of cultures grown on gelatin. The length of these bacilli is about two to four times the breadth. Some of them are somewhat curved (Durham). It is non-motile. It stains easily with all the basic aniline dyes, but loses its colour very rapidly when treated with alcohol or other decolourising agent, and is not stained by Gram's method. The absence of a fixative agent makes the bacteriological examination of tissue sections at present an impossibility. It readily emulsifies, that is to say the individual cocci are very loosely bound together and separate on being stirred up in a drop of water, unlike, for example, the plague bacillus in this. This property makes it very satisfactory in agglutination experiments. Its usual form is that of a coccus. Dr. Gordon has described flagella.

The micro-organism grows best in nutrient material, the alkalinity of which is slightly less than human blood, and at a temperature of from  $37^{\circ} \text{C.}$  to  $38^{\circ} \text{C.}$  It fulfils Koch's postulates at all points.

On a sloping surface of  $1\frac{1}{2}$  per cent of peptone agar, at a temperature of  $37^{\circ} \text{C.}$ , its colonies become visible to the naked eye in from 120 to 125 hours after inoculation from the human spleen. They first appear as minute, transparent, colourless drops on the surface of the agar. In about thirty-six hours they assume a transparent amber colour, and, increasing very slowly in size, become opaque in from four to five days from their first appearance. No liquefaction takes place. The colonies retain their vitality for over three months although they do not increase after two months. They cease to grow at  $18.5^{\circ} \text{C.}$ , and die if kept long at a moist temperature below  $15.5^{\circ} \text{C.}$  they live, however, for a long time in the dry state. They do not grow as primary growths on agar having an alkalinity in excess

of the blood. They can also be cultivated on gelatin and in bouillon in the former very slowly at a temperature of 22° C. without liquefying, in the latter they give rise to a general and increasing opaqueness, commencing on the fifth or sixth day, and afterwards forming a white precipitate consisting of these cocci, without forming a surface pellicle. They can be observed in fresh splenic substance, in the liver, kidneys, and, during life, in the blood of men suffering from this fever.

**Morbid Anatomy.**—Of the morbid anatomy of Malta fever there is not very much to be said. The principal appearances found on post-mortem examination are those due to fever, accompanied by a high temperature, and the presence of some irritating poison in the blood. The serous, muscular, mucous and submucous layers of Peyer's patches if examined under a low power, are found normal; and the epithelial layer is continuous over the whole surface of the gland. Under a higher power any morbid changes are found restricted to the mucous and submucous layers, and consist in a slight proliferation of the cellular elements. The small intestine is usually pallid and anæmic, except in the duodenum and upper part of the jejunum, where the mucous membrane may be more or less congested; in the more severe and chronic cases this may be accompanied by atrophy of the lower portion of the ileum. The large intestine is frequently extremely congested, especially the cæcum. The mesenteric glands are but slightly enlarged. The spleen is usually very much enlarged, dark on section, and the pulp soft and friable. It may weigh as much as sixty ounces, the average weight is eighteen ounces (Bruce). An appearance of intense congestion is seen on section, the sinuses being enormously distended with blood.

The liver is congested, and presents a pigmented appearance on section; and there is small round-celled infiltration between the lobules.

The kidneys are usually congested, with slight signs of hæmorrhage into their substance. The capsules are easily separated.

**Period of Incubation.**—The conditions in which Malta fever occurs often render it very difficult to arrive at a definite conclusion as to the period of incubation. Undoubtedly we have some few observations shewing with tolerable accuracy the time that has intervened between the exposure to the cause and the invasion of the illness. Charron states that six days after the 100th Regiment occupied Verdala Barrack in Malta cases of this fever began to be admitted to hospital. Marston says that ten days is the probable incubation-period, and gives two cases to justify his conclusion. These are instances no doubt in which the fever has been somewhat sudden in its onset; but there are many cases in which the attack comes on so slowly and insidiously that it is impossible to fix any limit. Dr. Johnstone concluded that the incubation of Malta fever is about fourteen days. Col. Davies writes: "As we are at present ignorant of the path of infection in man, we must assume that incubation may be as short as about a week, and may be as long as about five weeks according as the infection is by inoculation or by feeding. But consider-

ing the very much smaller doses of pathogenic material likely to be actually absorbed than those used experimentally in the laboratory, it seems probable that not less than a fortnight should be regarded as a minimum period, and that the maximum period should be extended to six weeks at least." According to our present knowledge of this disease, we shall not be far out if we put the incubation period between six and twenty days, and our most exact data give fifteen days as probably the commonest period (Bruce).

On account of the long duration and the constant relapses which take place during the progress and course of this disease, it is impossible to state whether one attack confers an immunity from a second. Col. Bruce is of opinion that such is the case.

**General Symptoms.** The invasion of the disease may be sudden or gradual. The symptoms in the early stage are rather obscure. The attack is preceded generally by dyspepsia, languor, headache, chilliness, and great weakness, it is often accompanied with muscular pains. The preliminary stage is usually marked by loss of appetite, often by headache and backache, but seldom by rigor or vomiting. Symptoms of gastric derangement manifest themselves at an early period, and persist more or less to the end. After a few days the patient suffers from nausea, sometimes even vomiting; his bowels are generally constipated, though there may be diarrhoea. He feels chilly and feverish, and recognises that his illness is increasing day by day.

In the more severe forms intense frontal headache is present, with enlargement and tenderness of the spleen. The patient's lassitude and debility become so great that he ceases to take an interest in anything; he loses his appetite altogether, and throughout the whole day and night he remains hot, thirsty, ill, and desponding. There is sometimes an extraordinary feeling of restlessness, which is frequently associated with insomnia. These symptoms may decline after a variable period, rarely less than a week, more frequently extending to two or three, when the patient fancies himself convalescent. But in a day or two relapses occur, nausea or vomiting returns, with loss of appetite and constipation, which may be followed by diarrhoea of a dysenteric character, the stools are devoid of any offensive odour, they may contain mucus and blood, but they are usually dark-coloured, and are never like those seen in typhoid fever. Muscular pains increase, the patient now becomes very anæmic, and his spleen is enlarged and painful on pressure.

In the more severe cases many or all of the preceding symptoms are aggravated, the headache becomes so intense as to be scarcely endurable, and the drowsiness may merge into stupor with low muttering delirium; the prostration is extreme; the lungs become congested, and readily take on a low form of inflammation, there may be epistaxis or sometimes considerable hæmoptysis. The pain in the limbs may develop into very decided rheumatism, with effusion into the joints. Endocarditis or other complications may supervene, and death ensue at almost any period.

**Digestive System.**—The symptoms of gastric and intestinal catarrh



manifest themselves at an early stage, and persist more or less to the end. The tongue is coated, white with red edges, and the papillæ are prominent at the base, it is large, flat, and flabby, and sometimes marked with the impress of the teeth. As the disease advances the tongue becomes more or less coated in the middle, and red at the tip and edges. Vesle has found this condition so constant that, so long as it remains, he never considers a man free from the liability to relapses.

The tonsils are often enlarged and swollen; the pharynx congested and occasionally ulcerated. The gums may be spongy, and may bleed freely; sometimes they are raw, sore, and slightly ulcerated. The palate is at times coated with an aphthous deposit, but there does not appear to be any inclination for this to spread. There is generally some uneasiness at the stomach, with nausea after food, but vomiting in the early stage of the fever is uncommon, and betokens either a severe attack or the early stage of a relapse. The appetite varies; when there is no nausea it is usually good.

The bowels are, as a rule, constipated, particularly in the milder cases, but there are many exceptions to this; they are seldom relaxed, often confined, and as often as not the patient suffers from diarrhoea, the evacuations being as described above. The abdomen may be tympanic, but this is unusual. The spleen is always enlarged, and pressure over it causes pain, even in those cases which are otherwise convalescent. The liver is sometimes enlarged, and may be tender on pressure, but in my own experience the enlargement of this organ is not constant or easily demonstrated. When pain is complained of it is invariably in the left hypochondrium and not in the right.

*Respiratory System.*—There is a very general liability to bronchial and catarrhal affections. About the end of the second or the commencement of the third week evidences of congestion of the lungs appear, the apices being the parts chiefly involved. The severity of the cough and expectoration are generally out of all proportion to the physical signs. On auscultation sibilant, mucous, and rhonchal râles are heard, on percussion there is somewhat diminished resonance. This, in severe cases, may be followed by congestion of the lower and posterior parts of the lungs, rapidly passing into pneumonia, accompanied by pleurisy and effusion; in almost every case it occurs on the left side. The dyspnoea and the amount of blood in the sputa are out of all proportion to the conditions found on physical examination. In the more severe forms of the disease this inflammation assumes a chronic character, and chronic pulmonary tuberculosis may follow.

*Circulatory System.*—Palpitation is by far the most common symptom. With the least excitement the heart beats with unusual rapidity and hæmic murmurs become audible. The pulse ranges from eighty to ninety beats per minute, and seldom exceeds this during the first period of the disease; during the later stages the pulse gains in frequency and loses force. Purpura frequently complicates this disease, and epistaxis, hæmoptysis, and bleeding from the gums are common. The red



Corpuscles as a rule fall from 5,000,000 per c.mm. to about 500. The white blood-corpuscles in most cases are normal in (Bruce).

*Temperature.*—The temperature curve in Malta fever is extremely irregular; so much so, that it is impossible to present any one case or chart as characteristic of the disease. In the early stages the temperature usually presents a continued form of fever, with exacerbations of temperature in the evening not exceeding one or two degrees, the temperature ranging between  $102^{\circ}$  and  $104^{\circ}$  F. In uncomplicated cases this condition lasts for a week or ten days, and the normal temperature is reached, and convalescence is established. In less favourable cases, when relapses occur after an interval of ten or twelve days, a second rise of temperature takes place, lasting about ten or twelve days; after which the normal is reached again. This may be followed by another relapse with a somewhat longer interval, and then by a shorter period of fever; after this the temperature again becomes normal, and with comparatively few exceptions this disturbance ends. Frequently in the secondary stages of the fever the temperature, during the axillary periods, presents the remittent form. In the early morning and at noon the temperature in the axilla and under the tongue is most frequently between  $97^{\circ}$  and  $101^{\circ}$  F.; but in the afternoon it rises more or less, generally from two to four degrees, and continues high until midnight, or perhaps a little later, when defervescence sets in with perspiration (Veale). In fatal cases the temperature usually runs up rapidly, and shortly before death reaching  $110^{\circ}$  F.

*Nervous System.*—The face and expression are truly characteristic of this fever; the pallor, anæmia, weariness, and despondent manner mark the virulent nature of the poison and its effect on the nervous system. Delirium, as a rule, is confined to the more severe cases. Anæmia is frequently mingled with an excessive irritability which is associated with loss of memory.

In the secondary stage these symptoms become more conspicuous. The patient is weak, tremulous, almost timid, and ready to shed tears on the least provocation. More rarely one may observe aphonia, or a temporary loss of sensation or of motion in the extremities. These deviations from the normal state exist in various degrees: sometimes one, sometimes another assumes a special pre-eminence. The shock to the nervous system, after the graver attacks, remains for some time. The memory is considerably impaired, especially with regard to names, dates, or rather the chronological order of events; the power of concentrating ideas, or following out a train of thought, is temporarily destroyed, and but very slowly returns. We must not mistake the mental aberrations, the aphonia, anæsthesia, hyperæsthesia, and so forth, for symptoms indicative of permanent lesions of the brain or spinal cord (Veale). Neuritis, especially in the form of sciatica, is apt to occur.

*Genito-urinary System.*—One of the most painful complications of this fever is inflammation or neuralgia of the testicle; it occurs in about 15

per cent of the cases. The epididymis is the part most usually affected but not infrequently the body of the testicle is involved also. The inflammation usually subsides without any active treatment. The average daily quantity of urine passed is between fifteen and twenty-five ounces; it is neutral, or very slightly acid when passed: there is usually a deposit of lithates and phosphates, but, apart from pre-existing kidney disease, albumin is extremely rare. In very severe attacks bile may be present in the urine. Micrococci are present in the urine.

*Integumentary System.*—Pallor and anæmia are perhaps the most characteristic features in the early stage. A condition approaching jaundice may also be present, but this is unusual. Perspiration is profuse, and sudamina, in greater or less number, are almost an invariable accompaniment. Cutaneous eruptions, such as erythema, eczema, and erythema nodosum, are not uncommon in the secondary stage. Many patients complain of a tingling or pricking sensation in the face, forehead, or hands, without any condition to account for it, except perhaps the nervous state already referred to. The hair falls out in nearly every case, usually during the secondary stage when the rheumatoid pains and swellings are most severe.

*Articulations.*—The rheumatic pains rarely if ever occur during the early stages of the disease. There is no constancy in the order in which the joints are affected. Sometimes the small joints of the hand or foot suffer first. In my own experience the extremities were most frequently involved, and the ankle-joint by preference. The joints became exquisitely tender, not in consequence of the amount of effusion present which is often inconsiderable, but from the hyperæsthesia of the integument. The most painful of all the joints are the sacro-iliac, in which the least movement causes the most intense pain. In such cases every change of position is dreaded, and the patient lies for days in the same position, risking the formation of bed-sores, and resisting the desire to evacuate the bowels, in order to avoid the suffering that the movement entails. The tendo Achillis and the fibrous structures round the ankle-joint are frequently implicated and exceedingly painful; oftentimes the lumbar aponeurosis and the sheaths of the nerves issuing from the sacral plexus are affected, and the pain runs down the back of the thigh or radiates to its anterior surface. Occasionally, as in gout, the bursa over the patella fills with fluid and become painful; but, more frequently, painful, node-like swellings form on the ribs or on their cartilages, or even on the sternum itself; these have been observed in patients who had not presented a sign of syphilis, either congenital or acquired.

As the blood-serum of patients with Malta fever agglutinates the *M. melitensis* in a specific manner, this test should be employed for the recognition of the disease and its differentiation from other fevers.

*Mortality.*—The immediate mortality from this disease is small. Col. Bruce (2) states that it is not above two per cent, and my own experience confirms this. Danger, however, is to be apprehended from continuously high temperature, and from such complications as

pneumonia and endocarditis. Excessive anæmia may lead to fatal syncope.

**Treatment.**—The only principle on which we can treat this fever is the rational one of supporting strength and combating symptoms as they arise. It has hitherto been found impossible by any remedial means to arrest the disease. In the early stage, if the patient suffer from constipation, some mild laxative may be given. Except at the very beginning of the fever, a hot bath is scarcely to be recommended, as the depression produced by the disease is already sufficiently well marked.

To relieve the nausea and vomiting a draught of morphine and hydrocyanic acid repeated occasionally, or again a few minims of chlorodyne, generally prove useful.

For the diarrhoea, when the ordinary vegetable astringents have failed, and especially where the hæmorrhagic tendency has been a source of danger, the continued use of the tinctura ferri perchloridi seemed to be most beneficial. Ergot and ergotin have also been of service in arresting hæmorrhage when profuse. Opiate enemata are especially useful in checking the milder forms of diarrhoea, and are as a rule extremely grateful to the patient.

Quinine has been given in doses varying from three to eighty grains daily, but without any beneficial effect. It neither arrests the progress of the fever nor limits the night-sweats or the rheumatic pains.

The hypodermic injection of morphine, and the liniments of aconite, opium, and belladonna are useful in relieving the lumbar, sciatic, and articular pains, salicylic acid and the salicylates are quite useless; and the same may be said of blisters, which appear only to substitute temporarily one pain for another. Orchitis is best relieved by hot fomentations, to which belladonna or opium may be added, and by the support of the inflamed testicle.

In cases in which the temperature curve rises suddenly the application of cold is probably the best antipyretic. Cold sponging and the wet pack are useful in moderate cases; but when hyperpyrexia threatens, immersion of the body in a cold bath is necessary to save life. The bath should be at a temperature of 68° F., and its duration should be about ten minutes, if, however, the patient shew signs of great weakness he should be wrapped up in a dry sheet or a light blanket and put to bed: the temperature should be frequently taken, and the baths repeated as often as the temperature rises to 103° F. or above it. Should the pulse shew signs of failing, or if there be shivering or any other evidence of weakness, brandy or some diffusible stimulant should be given, and bottles containing hot water applied to the feet. The cold bath should not be used except in cases of hyperpyrexia of such intensity that death seems imminent and only to be averted by energetic treatment.

Antipyrin is useful when given in full doses at intervals of an hour, or two or three hours. It causes a fall of temperature in a short time, which however rises again as rapidly. Headache and muscular pains are

largely benefited by this drug, and in the early stages it removes sleeplessness.

Careful nursing is perhaps the most important agent at our disposal. Food should be frequently administered, and the patient enjoined to make an effort to retain it. In many cases food of a semi-solid nature will be tolerated when liquid food is rejected. The diet should be very light, food of the simplest and blandest description, such as milk, beef-tea, and chicken-jelly flavoured with a little lemon, being appropriate.

Stimulants in the early stages of this disease are not to be recommended. When required they are best taken in the form of iced Moselle and soda water given as an ordinary drink, which not only slakes the burning thirst of the fever, but also allays to a considerable degree the irritability of the stomach. When the object is simply to slake thirst, lemonade made from the fresh juice of the fruit ought to be given, as this prevents scorbutic symptoms.

After the acute stage of the fever has passed the diet may be varied as much as possible, rice and custard puddings, fish and white meat being taken; but the return to solid food must be gradual. Until the temperature has remained normal for at least a fortnight the patient should not return to his ordinary diet.

The isolation of persons attacked by this disease should be insisted on, particularly in its early stages; also the complete disinfection of all clothing, bedding, and excreta. Persons suffering from Malta fever should not be treated in the same wards of a hospital with others who have not contracted the disease. In the light of our present knowledge it is very desirable to treat this disease as an infective fever and to adopt the same precautions as in other infectious diseases.

Convalescence can rarely be completed without a change of climate: most patients rapidly regain health when transferred to this country. It is, however, essential that this transportation should not take place during the first stages of the disease, but when convalescence is partially established.

J. LANE NOTTER.

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## CHOLERA

History, Morbid Anatomy, and Clinical Features by Col. KENNETH MATEON, I.M.S., M.D., LL.D.

Etiology and Epidemiology by the late Ernest Hart, D.C.L., and the late Solomon C. Smith, M.D. Revised by J. W. W. STEPHENS, M.D.

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### SYNONYM. *Cholera Asiatica*

**Nomenclature.**—The Hippocratic term cholera was originally employed to indicate bilious diarrhoea. It has come, in course of time, to be applied to any violent intestinal flux, such adjectives as simplex, biliosa, nostras, infantilis, serosa, spastica, perniciosa, epidemica, being used to distinguish varieties. The qualifying adjective commonly added to the word cholera, in order to denote the disease which is the subject of this article, is founded on the circumstance that in some parts of Asia—or, more strictly, of India—it is perennially present; and that, when it makes its appearance in other countries and continents, it can always be traced back to its Asiatic birthplace and home. It is by this geographical title that serous, spasmodic, pernicious, epidemic cholera is known in all the languages of Europe. In India it is usually denominated by the vernacular term *haza* (Hindustani); other Eastern names are *Enterum Funder* (Tamil), *Ookul Julah* (Deccan), *Funder* (Telugoo), *Huba* (Arabic), *Hoskowan* (Chinese), *Vishchika* (Sanskrit).

**Definition.** Cholera Asiatica may be defined as "a specific and communicable disease, in all probability due to a specific organism, prevailing epidemically in some parts of India, and from time to time diffused throughout the world. It is characterised by violent vomiting, purging, cramps, collapse, and suppression of urine, followed by febrile reaction, case-mortality about 50 per cent."



**History and Geography.**—The authentic history of Asiatic cholera dates from the year 1817, when it broke out violently in Lower Bengal, and became the subject of close and exact observation. There is every reason to believe that previous to that date the disease prevailed in India, and spread at intervals throughout Asia as it does now; but it is very doubtful whether it overstepped Asiatic limits. Certain passages in Sanscrit, Chinese, Arabic, and Greek medical literature have been supposed to refer to it; but the descriptions of all writers before the nineteenth century are vague, and vary as the colliquative, spasmodic, febrile, or prostrating features of the malady chiefly arrested attention. Cullen, for example, placed the disease among the spasmodic neuroses, and it cannot excite surprise that less learned and accurate physicians should have seized upon partial aspects of it to name, class, and describe it, thus creating difficulties of identification. It seems certain, however, that Portuguese, Dutch, and English physicians found the disease prevailing in India and its dependencies in the fifteenth, sixteenth, seventeenth, and eighteenth centuries; and when the outbreak of 1817 occurred it was recognised as a severe manifestation of a familiar scourge. Since 1817 Asiatic cholera has been watched with keen interest wherever it has prevailed; and the facts relating to its prevalence in India and elsewhere have been recorded with great minuteness and care. Voluminous as these records are, the story of cholera is a very simple and singularly interesting one. It presents the pictures of a deadly disease prevailing perennially in certain parts of India, which have been recognised as its home or field of endemic lodgment, where it waxes and wanes, but never altogether disappears; and of a dread epidemic taking its departure from its endemic habitat, after a recrudescence of more than usual severity, and diffusing itself along the ordinary routes of commerce and pilgrimage throughout the inhabited world. The history of cholera is thus a tale of repeated invasions, presenting a remarkable similarity. It is not easy to define with exactitude the endemic centre from which these invasions have proceeded: some authorities assert that there are several such centres in India; the principal one is undoubtedly the delta of the Ganges and the vast creek and river-netted alluvial plain which lies south of its confluence with the Brahmaputra. How far the endemic area extends up the Gangetic and Assam valleys it is difficult to say: or whether other deltaic regions in India, as of the Godavari and Kaveri rivers, are also endemic areas. It has been asserted that the disease is endemic in Bangkok, Canton, Shanghai, and perhaps other parts of Siam and China. It is important to note that, even in its endemic haunts, cholera presents most of the features which characterise its epidemic facies. It rises and falls, and travels; and if we carefully study particular tracts of country, we shall find that the disease presents a succession of outbreaks and an aspect of grouping very similar to what is observed in Europe when the disease visits a susceptible place and people in a favourable season.

It is observable that every departure of cholera beyond Indian limits



has been preceded by an outbreak in India of marked and unusual violence. Its westward diffusions have naturally attracted most attention; but eastern diffusions have also occurred—to the Straits Settlements, Siam, China, and Japan—which have not been so carefully investigated. The western invasions have taken place by three routes, namely, (1) through Afghanistan, Persia, and Central Asia, to Eastern Russia, along trade routes crossing or bordering the Caspian Sea, and thence into the interior of Russia along the Volga; (2) by the Persian Gulf to Turkish Arabia and Persia, thence to Turkey in Asia, and along or across the Black Sea to Constantinople and the Danube; and (3) by the Indian Ocean and Red Sea to Aden and Mecca, thence to Egypt and the countries bordering the Mediterranean. The disease prefers a land route to a sea route, and has sometimes travelled westwards by more than one route.

Seven distinct invasions of Europe took place during the nineteenth century. The outbreak of 1817 reached, but did not enter Europe. It covered India in 1818; found its way to Mauritius and Burma in 1819, reached Arabia, Siam, Malacca, and China in 1820, prevailed in Persia and Asiatic Turkey in 1821, and got as far as Tiflis and Astrakhan in 1823. There its westward march ended.

The first European invasion covers a period of thirteen years—1826-39. During the first three years India was extensively overrun by it; in 1829 the disease was carried by the Central Asian route through Kabul, Herat, Bokhara, Khiva, and Orenburg, as far as Nijni-Novgorod; in 1830 it travelled through Persia and by Resht, Tabriz, Tiflis, and Astrakhan to Southern Russia, eventually reaching Moscow. Russia and Poland were then occupied, and in 1831 Northern and Central Europe; in 1832 it invaded the United Kingdom and America, and in 1833 France, Spain, and Portugal; in 1834 Italy and North Africa suffered, and the disease lingered in Europe till 1839.

The second European invasion commenced in 1840 and ended in 1851—eleven years. Cholera was carried to China by our troops, and after raging severely in that empire, was conveyed by trade routes into Burma, Yarkand, Turkestan, and other parts of the Central Asian plateau. It broke out in Persia in 1845, in Arabia and Turkish Arabia in 1846, it reached Eastern Russia in 1847, and in 1848 it spread through Europe, visiting the United Kingdom, and reaching America *via* New Orleans from Havre. This epidemic subsided in 1851.

The third European invasion covered nine years—1848-57. It is thought by some authorities to have been a recrudescence of the cholera of 1840-51. During 1848-50 the disease ravaged India extensively; in 1851-52 it spread through Turkish Arabia and Persia, and reached Russia; in 1853 Asiatic Turkey and Northern Europe suffered; in 1854-55 the rest of Europe, Great Britain, and America were invaded. This outbreak, which died out in 1856-57, was the cholera from which the army of the Crimea suffered; and it was during this epidemic that

certain celebrated observations were made upon the agency of water in cholera diffusion.

The fourth European invasion of 1863-67 took place through Arabia and Egypt, as well as by way of Persia, the Black Sea, and the Caspian. The disease occupied Europe in 1865, and in 1866 it prevailed in Britain and America.

The fifth European invasion commenced in India in 1867—the year of the celebrated Hardwar outbreak—and lasted till 1873. Europe was reached by the Persian and Turkish-Arabian route, and during the years 1870-73 the disease raged in Europe and also in America, which was reached through New Orleans from Jamaica.

The sixth European invasion, dating from 1879, took place in Mecca (1882) and Egypt (1883). The countries bordering the Mediterranean suffered first and most, and the disease lingered in these till 1887. Indeed an outbreak in Paris in 1892 is considered to have been a survival of this epidemic. It was in Egypt, in 1883, that Koch discovered the bacillus which has formed so prominent a feature of cholera research in recent years.

The seventh European invasion of 1891-95 is remarkable for the unprecedented rapidity with which the disease travelled westward and overspread Europe. Beginning in Bengal in 1891, it raged in Upper India in 1892, and in the same year ravaged Kashmir and Kabul, travelling rapidly through Persia and Central Asia, and spreading over Northern and Central Europe. There was a violent outbreak at Hamburg, which has so frequently endured severe visitations. Cases occurred in English seaport towns, but the epidemic did not penetrate inland. In 1893 sharp outbreaks occurred at Hull, Grimsby, and Yarmouth, and in many adjoining inland localities; but this country as a whole escaped. This is the last occasion on which Asiatic cholera has visited Great Britain. In 1894 the disease continued to prevail extensively in Europe and in Western Russia, Galicia, Belgium, Holland, and France. About half-a-dozen cases were discovered at intervals in English seaports, but no spread either in these or inland took place. The epidemic subsided and disappeared in 1895. In 1896 Egypt and the Sudan were severely visited, but Europe remained exempt until 1904. A severe and extensive outbreak occurred in India in 1897—a year of widespread and grave famine—but no epidemic extension took place beyond Indian limits. In 1898 and 1899 India was comparatively exempt from cholera, but in 1900, in association with another and worse famine, the disease broke out with unusual virulence, and rapidly covered the whole Empire. This was the commencement of an epidemic which invaded many countries east and west. Kashmir was visited in 1900, and Japan in 1901. The disease appeared in Arabia in March 1902, and broke out among the pilgrims at Mecca and Jeddah. It crossed the Red Sea to the Italian province of Erythrea, and prevailed in Egypt from May to September. Cholera was also prevalent in the Dutch East Indies, Singapore, Borneo, China, Japan, the Philippine Islands, Formosa, and in

Syria and Persia. In 1903 Syria and Persia still suffered, and the disease spread eastward to Palestine, Asia Minor, and Mesopotamia. It continued to rage and spread in the Far East. In 1904 the Eastern outbreak continued, and involved Asiatic Turkey, Persia, and Russia. The invasion of Russia came across the Caspian; the tide of cholera reached Astrakhan, Saratov, Samara, and Nijni-Novgorod. In 1905 the disease continued to prevail in certain parts of Eastern and Southern Russia, but information on the subject is, owing to the disturbed state of the country, very scanty and vague. Cases occurred in Marienburg, Hamburg, and Berlin. Stringent measures were adopted to prevent the spread of the disease, and apparently with success.

From this cursory sketch it is evident that human intercourse and agency are the cardinal factors in cholera propagation; and the main question which has agitated the public mind, and engaged the attention of conferences and commissioners during these years, is whether the progress of cholera can be stayed by stopping communication between infected and non-infected places by means of a system of quarantine. This question resolves itself into two subsidiary questions, namely, whether quarantine be feasible and effective; and, if so, whether the disturbance of social life and interruption of commerce which it implies be justifiable. Unfortunately these questions have been chiefly debated on theoretical grounds, and have mainly turned on whether the disease be personally communicable or the reverse. Sufficient experience has now been gained to render a solution of the question possible on the surer basis of natural experiment. As regards inland quarantine, the experience gained by numerous trials in India and Europe has resulted in almost uniform failure; and when the difficulties of imposing a rigid quarantine and the chances of evasion are considered together with the possibility that dissemination may be effected by other agencies than human—by animals, birds, and insects, or by wind and water—it is not strange that the disease has so often overstepped the most rigid cordons. Quarantine was abolished in England in 1896. Maritime quarantine presents easier postulates, and has been attended with more success; but ships, unless crowded with emigrants, pilgrims, or soldiers under unsanitary conditions, are not such good porters of cholera as caravans, armies, hordes of pilgrims, and unsavoury travellers by road and rail. The policy of detaining masses of men in unwholesome lazarettos, subject to infection by new arrivals, has certainly proved disastrous; and a system of accurate and early information, careful inspection, isolation of the sick and suspected, and sanitation general and special, has been productive of greater benefit than any wholesale attempt to hinder the movements of men and merchandise. This is the manner of dealing with cholera, plague, and yellow fever which has been successfully practised in England for many years.

There are certain parts of the earth's surface, more or less insulated, which have not been visited by cholera. The most remarkable are the Andaman Islands in the Bay of Bengal, Réunion, Australia, New

Zealand, and other islands of the Pacific, the Cape of Good Hope and West Coast of Africa, the interior of the African continent, St. Helena, Ascension, the Azores, Bermudas, West Coast of South America, Orkney and Shetland Islands, Iceland and the Faroe Islands, and the colder parts of Europe, Asia, and America. This list is, moreover, by no means exhaustive. There are certain localities in all countries which have seldom or never been visited, while epidemics have prevailed around; and in any outbreak even in India, the places and persons attacked are always a minority of the whole. Even in Calcutta, the head centre and perpetual home of cholera, there is a quarter of the city which possesses as complete an immunity from the disease as Iceland. No better illustration than this could be given of the power of sanitation to extirpate cholera. A study of the statistics of European and native troops and prisoners in India has made it clear that during the last half-century a great abatement has occurred in the incidence and mortality of the disease. This satisfactory result must also be placed to the credit of improved sanitation, general and special.

K. M.

## ETIOLOGY AND EPIDEMIOLOGY

Cholera, as is now almost universally accepted, is due to a living contagium—Koch's cholera bacillus—which, growing in the intestines of the patient, causes death partly by the effect of the toxins produced by it and partly by the profuse purging which it sets up. The further etiology of the disease resolves itself into two factors—first, the means by which the microbe gains access to the body; second, the conditions which render the body susceptible to the microbe. Of the first of these we know much, of the second little.

*Mode of Access.*—It is certain that cholera is not contagious in the ordinary sense of the word. Cholera cannot be caught by contact, and although nurses and those who attend to the sick are often affected in larger proportion than others, this is readily explained by the fact that unless constant care is exercised in regard to cleanliness of hands and utensils they are much more exposed than are others to the known and recognised mode of infection, which is by the mouth. All evidence goes to shew that the infection of cholera to take effect must be swallowed.

Now, as in all zymotic diseases, the *materies morbi*—the *contagium vivum*—greatly increases within the body of the patient during the progress of his malady. During the disease a minute amount of infectious material grows into an amount capable of giving the infection to thousands; and, in the case of cholera, this infectious material finds its exit from the patient's body in the discharges caused by the disease.

The study of the etiology of cholera, then, is to a large extent a study of the steps by which matter that has left one patient so gains access to some article of food as to be swallowed by some one else.

It is conceivable that in the presence of a great abundance of the infection it might be inhaled in the form of dust. Of this, however, there

no evidence. It is with food and drink that it commonly gains access to the human body. Well-authenticated instances are related in which flies have appeared to carry the infection from cholera dejecta to milk in various articles of diet; and Haffkine has detected cholera bacilli in specimens of sterilised milk, exposed in new vessels, to which flies were admitted free access during an attack of cholera (1). The use of cholera-infected water for washing cooking utensils and articles used in preparation of food is another mode of local distribution; especially with regard to the spread of the disease by milk. In the case of nurses and those who attend to the sick, or have charge of the dead, the cholera poison may, as a result of want of strict cleanliness, be transferred to the mouth by the fingers, either directly or by means of food.

But the great, the persistent, and the almost universal mode by which the cholera germ gains access to the body is in the drinking-water. This is now so well recognised that it is unnecessary to go again over the evidence by which this has been proved to demonstration. It may, however, be well to refer to a few of the classical examples of this mode of cholera distribution.<sup>1</sup>

A full account of the case of the Broad Street pump, which was investigated by Dr. Snow, is to be found in the *Report of the Committee for Scientific Inquiries into the Cholera of 1854*. The relation between the incidence of cholera and the source of the water-supply to different parts of London is described in the *Report of the Royal Commission on Water-Supply, 1869*. The outbreak of cholera in the East End of London in 1866, which was traced to the supply of specifically contaminated water, is described by Mr. Netten Radcliffe in the *Report of the Medical Officer to the Local Government Board, 1866*; and the great outbreak of cholera in Hamburg is described with full statistical detail in the *Report of the Medical Officer to the Local Government Board, 1892-93*.

There is a good deal of evidence to shew that water does not act as a mere diluent and distributor of the cholera poison, but that under certain conditions the cholera bacilli grow and for a short time increase in virulence during their sojourn in this medium. The persistence of cholera in a district is indicative of more than a single pollution of the water-supply, and generally points to a persistence of some insanitary conditions which favour repeated infection.

It is not always the case, however, that the infection is conveyed directly from man to man by means of water. Where we find sudden outbursts of disease affecting large numbers of people drawing their water-supply from a common source, some direct and wholesale fouling of the supply is generally the cause of the mischief. But much more commonly, especially near its endemic home in India, cholera does not occur in great outbursts; small local epidemics arise, die down, and then recur. The cholera bacillus—existing, as we must presume, in the foul soil—is

<sup>1</sup> In how wide a sense the term "drinking-water" may properly be applied is indicated by the alleged dissemination of the cholera poison by means of oysters which had been exposed to the affluence of sewage.



now and again washed into the wells, and so sets up disease in those that draw their water from them. The key, then, to this side of the etiology of cholera is to be found in the habits of the people, and the degree of care or want of care they exercise in the protection of their water-supplies.

The natural home of cholera is a land of foul water. In Lower Bengal, where cases are reported every month in every year, an inquiry into the habits of the people, and the condition of the tanks from which they largely draw their water-supply, is sufficient to show how constant are the opportunities both for food and water, especially the latter, to be exposed to faecal contamination. In many of the towns of Southern Europe, also, which have most markedly suffered from the ravages of cholera (among these Naples and Marseilles may be specially mentioned) it has been demonstrated that while the water-supplies had been contaminated, the habits of the people had intensified the evils resulting from this cause. On the other hand, our own practical immunity during the epidemics which have broken out in Europe since greater attention has been given in England to the securing of pure water, compared with our great mortality from cholera in earlier epidemics, together with the great lessening of the cholera mortality in those towns in India which have obtained pure water while epidemics have continued as of old in surrounding districts, both tend to shew that when the habit of drinking water which has been exposed to chances of faecal defilement is once broken cholera fails to take root.

*Individual Susceptibility.*—The etiology of cholera is not, however, completely explained by the statement that it depends on the ingestion of cholera-infected water; another condition is also necessary, namely, the susceptibility of the individual. Considerable differences exist in the habits of the various members of every community; thus, it often happens that even where the habits of the majority are foul, a few are protected from receiving the infection by the greater cleanliness and propriety of their lives. Yet many fail to sicken, although they are known to have swallowed the very infective matter which at the same time is producing cholera in others. We have proof of this in every widespread water epidemic; the number of those who swallow the poison must in these cases vastly exceed the number of those who are attacked by the disease. Macnamara gives an instance in which a vessel of drinking-water was accidentally polluted with fresh cholera excreta, and after being exposed to the sun all day the water was partaken of by nineteen persons: of these five only subsequently suffered from cholera. It seems clear that the inhabitants of the areas in which cholera is frequently present, notwithstanding habits which expose them continually to chances of infection, are much less frequently attacked than new arrivals in the districts, much less, for instance, than Europeans, although when attacked they succumb more readily.

On the other hand there is a good deal of clinical evidence—of a nature, however, that can hardly be brought to the test of statistics



to shew that any disturbance of the balance of the digestive organs, especially the dyspepsia common among drinkers, and the looseness of bowels often brought on by eating over-ripe or decomposing fruit, distinctly tends to leave the patient open to the cholera infection—that fact an active gastric digestion and a healthy intestinal mucous surface form a considerable bar to attacks of cholera.

So far we have considered the etiology of cholera as it affects the individual. We have shewn that although the condition of the patient is an influence on the effect of the attack, the immediate factor in the production of cholera is the swallowing of an infection which has come, directly or indirectly, from the dejecta passed by another patient suffering from the same disease; thus we have demonstrated that cholera may properly be called a filth disease: not that filth, unless infected with cholera, can cause the disease, but that, without the filthy habits which bring about the consumption of food or drink befouled by man's dejecta, cholera cannot be transmitted.

*Epidemic Prevalence.*—This view, however, of the etiology of cholera by no means explains the occurrence of epidemics, nor the tendency of these epidemics at varying periods to spread beyond the normal confines of the disease, to extend into areas which for long series of years had been entirely free from it, to advance stage by stage, and thus to march round the globe; then to retire, and for an uncertain period either to be latent or to be confined within the endemic area. To understand this peculiarity of cholera, it is necessary to bear in mind the various factors which aid in the dissemination of the disease, and to recognise that it is the coincidence of many factors which sets cholera on the march.

Within certain areas in India cholera is endemic, especially in the country of the Lower Ganges. If, however, we examine carefully the incidence of cholera within the endemic area, it becomes obvious that, although in every district deaths from it may be reported every year and every month in every year, still the incidence of this mortality is by no means evenly distributed; even within the endemic area cholera wanders about, one village after another being attacked and then left at peace for a time. It seems as if there were the same tendency for these outbursts to die down within the area as there is outside it; but that in consequence of the great facilities for reimportation, and of the condition of the soil, which makes it possible for the germ to maintain its vitality and carry on the saprophytic phase of its existence for a considerable time, the disease frequently crops up again—whenever, in fact, there is a sufficiency of susceptible people for it to prey upon, and whenever accident introduces it afresh into the drinking-water.

It is important to bear in mind that the highest mortality from cholera does not occur in the parts in which the disease is permanently endemic; this points to the probability that dwellers within the endemic areas attain some degree of immunity from the infection.

*The Spread of Epidemic Cholera.*—One of the most striking peculiarities of epidemic cholera, when it oversteps the bounds of its endemic

area, is its tendency to advance along fairly definite tracks ; to go from town to town, from country to country ; to attack each fresh district with enormous virulence at first ; then, in a short time, to become much modified in intensity, subsiding altogether in about three months to return again the next year, and perhaps the year after ; then again to die out entirely till it is introduced afresh, passing on meanwhile to some other place where the same course is repeated. The study of the epidemiology of cholera thus involves that of the modes by which the disease is carried from place to place, the influences which favour its dissemination, those which favour or retard its taking root in fresh localities, together with those curious periodic variations of intensity which, for the sake of a phrase, are sometimes attributed to "epidemic influence."

There can no longer be any doubt that cholera is disseminated by human intercourse. The march of cholera coincides with the march of man, and it is carried from place to place either by infected man or by cholera-tainted clothing. The part played by pilgrimages, *e.g.* the pilgrimage to Mecca, is well known, and severe outbreaks and wide dispersion have often followed on such movements of large bodies of men. There seems no practical limit to the distance to which it would be possible to transmit the infection in a bundle of imperfectly dried rags soiled by cholera excreta ; man, however, can but carry the disease so far as he is able to travel between receiving the infection and being laid low. What we find, then, on comparing the march of the earlier epidemics of cholera with those that have occurred in more recent years is that whereas when travel was slow the disease swept steadily forwards, occupying the land as it advanced ; in later times it has bounded forward with long strides, occupying outposts far ahead of infected areas by means of railway and steamboat communication, and then, from these outlying foci of infection, has spread in both directions, coalescing perhaps at a much later date with the main body of the epidemic which has slowly advanced across country from the earlier centres.

Certain as it is, however, that man is the porter by whom cholera is introduced to any place, it must not be forgotten that its development in that place depends on insanitary circumstances, the chief condition necessary being the liability of the drinking-water to be contaminated by infected excreta. There are probably other but more obscure conditions still unknown to us.

It will thus be readily understood why cholera is so apt to be spread in epidemic form by wars and pilgrimages. Cholera may and often does travel along the tracks of ordinary trade ; but it never advances far unless along its path there be places where the sanitary conditions, some known others probably still unknown, enable the disease to take root and start upon its course afresh. When, however, as in the case of wars or pilgrimages, great bodies of men are camped out without any proper means of dealing with their excreta, or any assurance that their water supply remains untainted ; and especially when, as is the case in the

great religious pilgrimages which are recruited from within the endemic home of cholera, the men who form these camps carry with them those habits and customs which, within that area tend to make cholera permanently endemic, then we find every condition fulfilled for the epidemic propagation of the disease.

Accepting the view that when cholera is introduced into new districts it is carried thither by cholera-infected rags, cholera infected food or cholera infected man, it becomes a matter of great importance to determine whether the last (namely, cholera infected man) can carry with him the germs, deposit them in fresh places, infect water supplies, and set up epidemics, without himself suffering from cholera and betraying its symptoms. Till a few years ago this question would have been unhesitatingly answered in the negative; and in fact it is in the belief that a man cannot carry cholera unless he himself suffer from it that the modern substitute for quarantine is founded, namely, the system of medical inspection and detention of invalids. Modern travel is conducted on so vast a scale, and the numbers moving from place to place are so enormous, that efficient quarantine is obviously impossible. It has been hoped, however, that if those actually ailing be sorted out the rest may safely be allowed to pass. Hence the modern system. The investigations of Koch and others tend, however, to throw some doubt upon the efficiency of such measures; and although they have appeared successful in preventing the disease from taking root in England, it is quite possible that the greater attention given to the purity of the water supply of our towns may have had a much larger share than our port sanitary inspection in giving us the exemption we have enjoyed. Koch has shown (3), and it has been shewn repeatedly at the observation stations which were established in Germany at the time of the epidemics in Hamburg in 1892 and 1893, that among those who had been exposed to the possibility of cholera infection, and who yet remained apparently healthy, there were individuals whose feces, although hardly diarrhoeic—nay, quite normal, yet, nevertheless, contained cholera bacteria. "It is now certain that among a number of persons who have been exposed to cholera infection the resultant cases may show the whole scale from the severest and rapidly fatal cases down to the mildest imaginable, demonstrable only by bacteriological investigation."

The determination of this point goes far to explain outbreaks of cholera in which the first apparent sufferers could be shewn not to have entered any infected district. The very first case has, in fact, not been recognised, maybe the patient has not known that he was ill, his dejecta have nevertheless, obtained access to the water-supply, and thus given rise to the outbreak. It is in this way possible to explain some of the isolated sporadic cases which have occurred in England, cases in which, notwithstanding the entire want of evidence of any connexion with any known focus of the disease, the characteristic micro-organisms have been discovered. But we cannot state positively that this explanation is the true one.

*Conditions determining Character of Outbreak.* — When the cholera germs have once been introduced into a district their fate will depend on various conditions. If they chance to gain access to a public water-supply they will, as has been shewn again and again, set up a sudden and widespread epidemic among the consumers of the water—an epidemic which breaks out simultaneously in different parts of the district, rages violently for a time, and if the infected water be cut off, stops almost as suddenly as it had begun.

If, however, the germs do not gain access to a general water-supply, but are deposited in the neighbourhood of the dwellings of the people, they will only set up small and localised outbreaks; in one part after another of a town, in one town after another, cholera will arise and soon die out, only to crop up again in neighbouring places, or even in the same place again; and thus an epidemic, never perhaps severe, may continue so long as to cause serious loss of life. The continuance of an outbreak of this latter sort depends upon conditions not as yet accurately defined; and it is obvious that, although a general water-epidemic has a sudden rise and a sudden fall, one occurring in a district which favours the development of foci of cholera, although it may rise as suddenly, will not terminate so quickly: it will rather set up a multitude of centres from which it will continue to spread as in the second mode, the mode in which it mostly shews itself in countries in which it is endemic during non-epidemic times—countries in most parts of which no such thing as a public water-supply, in the modern sense of the term, exists. It becomes then very important to inquire into the causes other than the infection of public water-supplies which favour the development of epidemic cholera; for it is certain that “in many districts of greater or less extent, the cholera has never reached any considerable or strictly epidemic development notwithstanding repeated importations of the poison” (4).

*Conditions favouring the Development of Cholera Epidemics.* — Hirsch says: “As there are certain local peculiarities which furnish the conditions for the endemic disease, so also there are certain factors residing in the circumstances of place or season, which are necessary to give potency to the cholera poison beyond its native habitat”; and he quotes Hergt as saying: “The rise of the cholera epidemic at any one place implies, besides importation of the contagium, certain local conditions of atmosphere and of soil as well. These conditions must be able at a given place to generate themselves and to disappear again.” The latter is an important qualification, for it appears certain that among the causes necessary for the development of cholera in an epidemic form, except when widely distributed by water, are some which are purely temporary, as for example those which are connected with season: and that a locality, which at one time may be capable of developing cholera in a most virulent form, may at other times be, comparatively speaking, protected from its attacks. Putting, then, on one side infection of public water-supply, which is capable of creating an epidemic in any place and

ny season, we have to consider the factors in the production of an epidemic not arising from that cause. Concerning these factors little is known. We may consider them under the following headings:—

(a) Altitude.—Elevated districts often remain exempt from cholera; the other hand valleys and low-lying areas are much more apt to suffer: in towns situated on a slope, or occupying different elevations, it is usually found that within the same town the higher districts are least affected. On the other hand, cholera has occurred at very considerable altitudes, and even sufficiently often in the higher parts of mountains to make it clear that the cause of the apparent variation of cholera with altitude must be sought elsewhere, probably in its relation to temperature, water-supply, and movement of ground-water.

(b) Relation to Rivers.—It has constantly been observed that not only does cholera follow rivers, which it should be noted are also commonly lines of traffic and centres for the aggregation of large populations,—two main factors in the dissemination of the disease,—but that it attacks places on the banks of rivers and even of small streams with peculiar severity. This again probably has relation to conditions of soil and density of population, as well as to the double function of rivers as drains and sources of water-supply.

(c) Character of Soil.—Cholera attains its greatest intensity on soils which are permeable to water, but not sodden with it, and are at the same time capable of retaining a certain degree of moisture within their interstices.

The relation, then, of altitude, neighbourhood of rivers, and character of soil may all resolve themselves into this—that cholera is most likely to take on its epidemic character on a soil which is porous, more or less charged with decomposing organic matter, moistened with water, and having its interstices filled with air. Emmerich and Gemünd have indeed shewn that cholera vibrios die on gravelly soil in seven days, while on naturally impure soil they multiply enormously and only die in the superficial layers in 15-81 days. On such a soil complete dryness or complete saturation, are inimical to cholera; while a falling groundwater, leaving the soil moist, full of air, and charged with organic matter on the surface, disposes to cholera; not only by favouring the trophic growth of the cholera bacillus, but also by facilitating its access to wells.

(d) Habits of Inhabitants.—Even amidst the conditions of soil and climate most favourable or most inimical to cholera, its prevalence largely depends upon the habits of the people; however largely present its contagium may be, it is harmless unless swallowed. Thus, among all the influences making for cholera, the most important are those habits of carelessness as to the cleanliness of food and drink, which make it easy for either the one or the other to be tainted with faecal material.

(e) General Sanitation.—As is the influence of the habit of cleanliness to the individual, so is that of general sanitation to the body corporate. Good drainage and good water-supply keep cholera at bay by

making it impossible for the faces of one person to gain access to the drink or food of another.

This brings us back to the keynote of the etiology and epidemiology of cholera, namely, the ingestion of infected water or infected food.

The act of swallowing the living contagium derived from the excreta of a previous sufferer from the disease is the immediate cause of cholera in the individual; while the means by which facilities are given for the growth of this contagium outside the body, for its widespread dissemination, and for its introduction into the food or drink of man, are the causes of cholera epidemics. While this is true, yet we are still far from explaining why cholera is epidemic at one time, and then at another completely disappears, for we have no ground for thinking that the known conditions of its dissemination have ceased to become operative during these periods of quiescence. The problem is indeed that which faces us in the consideration of the epidemicity of many other diseases, and is equally unsolved at present.

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#### BACTERIOLOGY OF CHOLERA

In 1883 Koch separated a characteristic curved organism from the dejecta and intestines of cholera patients, the comma bacillus; this he declared to be absent from the stools and intestinal contents of healthy persons, and of persons suffering from other affections. The organism was said to possess certain morphological and biological features which readily distinguished it from all previously described organisms. It was absent from the blood and viscera, and was found only in the intestines; and the greater the number, it was said, the more acute the attack. Koch also demonstrated an invasion of the mucosa and its glands by the comma bacilli. The organisms were found in the stools on staining the mucous flakes or the fluid with methylene blue or fuchsin,—and sometimes alone; by means of cultivation on gelatin they were readily separated from the stools. During his stay in India, in Egypt, and at Toulon, Koch had examined more than a hundred cases, and other investigators confirmed his statements. Numerous control observations



made upon other diarrhoeic dejecta and upon normal stools, were negative : the comma bacillus was found in choleraic material only, or in material contaminated by cholera. Soon other observers, however, described comma-shaped organisms of non-choleraic origin ; Finkler and Prior, for instance, found them in the diarrhoeic stools of cholera nostras, Deneke in cheese, Lewis and Millar in saliva. All of these organisms, however, differed in many respects from Koch's comma bacillus ; and gradually the exclusive association of Koch's vibrio with cholera became almost generally acknowledged. In 1886, indeed, Flugge maintained that the comma bacilli must be regarded as the cause of cholera, because they occur constantly and exclusively in this disease.

Koch described his vibrios as short, curved organisms, often arranged as spirals, the curvature of the individuals varied greatly, the latter being sometimes almost straight, and at other times nearly semicircular. Two commas may be attached so as to form an S, spirals, even of great length, may indeed be found. According to Kolle and Gotschlich, cholera vibrios may vary so much in (1) size, (2) curvature, (3) motility, that from morphological characters it is quite impossible to determine whether a particular species is cholera or not. They describe group A, short cocci like forms, group B, medium-sized forms well curved, *i.e.* typical vibrios ; group C, very long slender forms almost straight. Although morphologically so different, yet in all other respects they behave like true cholera vibrios. They possess the power of spontaneous movement in a marked degree, and readily undergo involution, becoming round and coecal or irregular in appearance. On gelatin plates at 22° C, after twenty-four hours, they form minute yellowish-white refractive colonies, the contour of which is not regular, but scalloped and undulating. As growth proceeds this irregularity of outline becomes more marked, and the surface of the colony partakes in this irregularity, and at the same time the colony as a whole becomes highly refractive as if beset with a number of fine glass spicules. Then liquefaction of the gelatin gradually begins, and the refractive colonies sink into its substance. This 'typical' appearance of a true cholera vibrio has, it is now agreed, lost the importance which was at first given to it, for it is recognised that true cholera may give an "atypical" appearance, and the diagnosis of true cholera vibrios no longer rests to a great extent on this appearance as it did in earlier days. Yet it is true that frequently typical colonies appear when cultures are first isolated from faeces, and that atypical colonies are more frequent in laboratory cultures ; and, as Kolle and Gotschlich remark, there is no other disease except cholera in which these strongly refractive colonies in considerable quantity can be got out of the faeces or contents of the gut.

Stab-cultures in gelatin are equally characteristic ; there is a whitish growth along the needle track with gradual liquefaction, which at first is most marked near the surface, so that a turnip-shaped depression is formed, the upper portion of which, by evaporation of the liquid, becomes filled with air. Liquefaction is comparatively slow, but after six days it

has progressed so far as to destroy the appearance just described. The extent of liquefaction of gelatin depends on the alkalinity and melting-point of the gelatin, apart from individual differences in vibrios from different sources. On agar-agar we have transparent colonies, opalescent by transmitted light, of a characteristic appearance; growth occurs on potato at a raised temperature only; milk is not coagulated. Koch's vibrio is capable of thriving in very dilute broth or peptone solution. On the latter especially the vibrios accumulate at the surface, often forming a pellicle. This property of surface growth is of the greatest practical importance, as will be seen later. Cholera is a facultative anaerobe, and grows best between 30° and 40° C. The optimum reaction of media, according to Wherry (37), is obtained with an alkalinity of  $\frac{1}{30}$  to  $\frac{1}{10}$  of a gram-molecule of NaHO or Na<sub>2</sub>CO<sub>3</sub> per litre. The cholera vibrio forms alkali on sugar-free media, but not if these are free from salt. On nutrose media containing sugars the cholera vibrio forms acid to about the same extent as *B. coli*, but acid is not formed on media containing dulcitate or erythrite (28).

**The Pathogenetic Properties of the Cholera Vibrio.**—Animal experiments, in so far as their aim was to reproduce a typical choleraic lesion, were not successful in Koch's hands; nor can those performed by Nicati, Rietsch, and van Ermengem be considered convincing. Subcutaneous inoculations and feeding led to no result; direct inoculation into the duodenum, with or without previous ligature of the bile-duct, frequently produced fatal diarrhoea with abundant vibrios in the dejecta, but since this result seemed to depend to a great extent on intestinal injury they are not free from doubt. Koch himself, indeed, asserted that he had induced a choleraic process by feeding guinea-pigs with pure cultures, after previous neutralisation of the gastric contents and injection of tincture of opium into the peritoneal cavity, in order to paralyse the intestinal peristalsis. Yet as other vibrios act in the same manner, these animal experiments have not established the specifically pathogenetic power of the comma bacillus. The sterile products of choleraic cultures administered to a guinea-pig will cause distinct intoxicative symptoms or death, as first shewn by Nicati and Rietsch; these symptoms, however, do not differ from those produced by many other bacterial toxins. Experiments on man have contributed towards establishing the infective nature of the cholera vibrios. Several cases are on record where, after swallowing of cultures of vibrios purposely or accidentally, severe symptoms and even death have followed, though in other instances the result has been negative or only very slight. Among these are the fatal case, in Koch's laboratory, of a physician working with cholera cultures; the fatal case of Dr. Örgel, of Hamburg, who accidentally swallowed some cholera material from a post-mortem on a guinea-pig; and the celebrated cases of Pettenkofer and Emmerich, who purposely swallowed cultures. The former suffered from diarrhoea only, while the latter had a characteristic and almost fatal attack of cholera. Other cases, it is true, are on record in which no result has followed the swallowing of cultures.

but against the positive cases they can hardly stand as of preponderating value, for, among other things, there is no proof that in these cases virulent cultures were used.

We must also point out that Haffkine's (13) anticholeraic vaccinations in India contributed much to establish this hypothesis. Haffkine was firmly convinced that the cause of cholera was one variable vibrio; and for the purpose of vaccination he used living cultures of that which he considered to be the choleraic vibrio. He originally prepared two vaccines, a weakened first virus, and a strengthened second virus; so that the principle of his inoculation was the same as that practised in the case of anthrax. Thus, in Calcutta he found that the mortality among the inoculated was 17·24 times less, and the incidence of cholera 19·27 times less, than among the non inoculated. The proof of the specificity of the cholera vibrio is, as we shall see, founded on other facts; it is, however, important to bear in mind the pathogenetic action of the true cholera vibrio on pigeons. Though the distinction is not absolute, yet it may fairly be said that a vibrio which is pathogenetic for pigeons by intramuscular injection is probably not cholera.

Pfeiffer demonstrated that the cholera vibrio possesses a single terminal flagellum, non choleraic vibrios may, however, possess several. Of more interest, however, is a peculiar chemical reaction which Koch pronounced to be characteristic, the so called cholera red reaction. On adding pure hydrochloric or sulphuric acid to a culture in peptone solution or in peptone broth, a pink or red colour (cholera red) appears. This reaction was discovered by Pohl, Bujwid, and Dunham in 1886 and 1887, and was explained by Sulkowski, who at the same time proved it to be of no specific value. Wherry (38) draws a distinction between the purple "indol reaction" and the vermilion coloured "cholera-red reaction." The formation of cholera red only takes place during the reduction of a nitrate containing medium. Thus, while a peptone solution dialysed free from nitrite will give after the growth of cholera vibrios, a deep purple indol reaction on the addition of pure sulphuric acid, the cholera red vermilion colour is not produced. If, however, a trace of nitrate be originally added to the medium, the cholera red reaction is obtained best after a few days' growth. The test should then be performed in this way, viz.: To a peptone solution dialysed free from nitrites 0·1 per cent of  $\text{NaNO}_3$  is added. The cholera organism is grown in 10 c.c. of this medium for three days, and then 0·5 c.c. of pure sulphuric acid is added. With regard to the diagnostic importance of this test we may say that a vibrio which does not respond to the test—under conditions where a true cholera vibrio does—is not cholera.

The result of much labour and argument expended on the attempt to find satisfactory distinctive characters of cholera has not proved successful, but there remain other methods. Pfeiffer, who never doubted the correctness of Koch's observations and deductions, recognising, nevertheless, that none of the proposed tests vouchsafe a certain diagnosis, introduced a novel method of distinguishing between true and false

cholera vibrios. It was based on the fundamental proposition expressed by Behring, that the serum of a protected animal is specific in its action—that is, if injected into an animal it confers on it an immunity only from the lesion against which the original animal had been protected. Pfeiffer therefore, rendered animals proof against a cholera vibrio, and then used their serum as a test. Its action being specific, the serum can counteract the effects of one species of vibrio only, and must be impotent against all others. His method of procedure is as follows:—

*Pfeiffer's Phenomenon.*—A serum must be used which is of high immunising value, e.g. at least 0.0002 gramme of the serum must protect a guinea-pig on injection of a mixture of 1 loop (2 mg.) of a culture of constant virulence ( $\frac{1}{10}$  of a loop—minimal lethal dose, distributed in 1 c.c. of broth). The injection is made intraperitoneally with a fine cannula into guinea pigs (200 grammes). If the reaction is now positive, the vibrios are transformed into pale spherical bodies which eventually are completely dissolved, and the animal survives. If it is negative, the vibrios multiply and the animal dies. The progress of the reaction is determined from time to time by taking out samples of the peritoneal contents by means of capillary pipettes. Such a serum can be prepared by injecting rabbits with sterilised cultures of virulent vibrios, thus by intravenous injections of 1 loop, 3 loops, 5 loops at weekly intervals, a potent serum is obtainable seven days after the last injection. Besides this method there is the complementary one of agglutination.

*Agglutination Test.*—While Pfeiffer's test depends upon the property of an homologous serum in producing a bactericidal or cytolytic effect, here the reaction is one of agglutination or agglomeration, and depends upon the law, the evidence for which we shall consider later, that the true cholera vibrio is only agglomerated by a serum obtained by immunisation with a true cholera vibrio.

The method of applying it in diagnosis we shall refer to later, we may here describe in a general way the mode of performing the operation. The serum is diluted with perfectly clear filtered salt solution (0.8 per cent) in various dilutions, ranging from 1:50 to 1:2000. One cubic centimetre of each solution is poured into a small test-tube, and then one loop (2 mgm.) of culture is rubbed up in each and thoroughly mixed. The tubes are kept for one hour at 37° C., and if the reaction is positive agglomeration or clumping should be evident to the naked eye.

We shall now discuss the evidence upon which we hold that these two tests are satisfactory, and indeed the only satisfactory, ones for determining whether a vibrio, whatever be its source, is or is not a true cholera vibrio. The evidence, as we shall see, is not based upon theoretical arguments as to the character of such reactions as these, viz., the bactericidal and agglutinating properties of an immune serum; but is based upon the result of a very exhaustive comparison of vibrios from many sources tested by these means. Thus, Kolle and Gotschlich have made elaborate comparisons of vibrios isolated from 73 cases of "cholera" in Egypt of these 59 were true cholera according to the tests mentioned above.

e a mixture of cholera vibrio and a cholera-like vibrio; 14 gave vibrios which were not cholera, and, moreover, and this is an important point, they all differed from one another except 2, and it is also important to note that the cases from which these 2 were isolated had no connexion with one another. With regard to the epidemiology of the cholera-like vibrios, in 4 cases there was no history, in 5 the cases were clinically and epidemiologically probably not cholera, while in the remaining 7 they were clinically and epidemiologically true cholera (and indeed from other cases in the same families true cholera vibrios had been isolated), and from 16 of these cholera vibrios as well as cholera-like vibrios had been isolated. Further, of these 16 cholera-like vibrios 5 had several flagella, whereas the cholera has only one, 1 was non-motile, 3 were fatal to pigeons on intramuscular injection resembling in this respect *V. metchnikovi*, which is not a true cholera vibrio, while 7 others differed morphologically and on agar plates from the true cholera vibrio and from one another. So that from these characters alone these vibrios were probably not cholera. Further, the evidence against cholera-like vibrios being causally connected with cholera lies in (1) that they occur among cases clinically and epidemiologically not suspected of being cholera; (2) that the cases in which they are found have no epidemiological connexion with one another; (3) that they differ among themselves. To consider now the evidence based on serum-tests upon which we can declare with certainty whether a vibrio is the cholera vibrio or not. Of 59 vibrios isolated from cases which clinically were cholera all behaved in exactly the same way to the serum-tests; that is to say, they all suffered dissolution on intraperitoneal injection, and were agglutinated *in vitro* by a serum prepared from true cholera vibrio, and, moreover, they all reacted in the same way to serum prepared from any one of their number; while, further, none of them reacted with a serum prepared from any of the 16 cholera-like vibrios, nor did any of the 16 cholera-like vibrios react with a serum prepared from any of the cholera-like vibrios. So that the *specificity* of the reaction is absolute, and is reciprocal between any two true cholera vibrios and their serums. These experiments, then, the result of many hundreds of combinations between vibrio and serum, may be summed up as follows—(1) Every true cholera vibrio reacts with a true cholera serum; (2) No true cholera vibrio reacts with a cholera-like serum; (3) No cholera-like vibrio reacts with a cholera serum; (4) Every cholera vibrio reacts with its own and homologous serums, but not with others. There is no question in these reactions of the occurrence of a group-reaction, for cholera-like organisms were not more influenced by cholera serums than by normal serums. It may be argued, however, that even granting that this last is true, it does not disprove that the 16 vibrios were not likewise the cause of "cholera." But against such a view Kolle and Gotschlich urge, and rightly so, that these vibrios differed among themselves and occur in few cases only, while in 59 cases vibrios identical among themselves were isolated, and also there is the fact that these cholera-like vibrios cannot be isolated in pure culture by direct inoculation, *e.g.* of agar



plates, as is possible with the true cholera vibrio, but can only be done by the peptone method (*vide* p. 457). We have already mentioned the epidemiological evidence against any causal connexion between cholera-like vibrios and cholera; the former probably occur simply as accidental concomitant saprophytes.

*Vitality of the Cholera Vibrio.*—The specific germs—Koch's comma bacilli—are shed in the stools from the body during the first days of the disease, and only these, or matter contaminated by them, as for instance the bed linen, vessels, latrines, soil or drinking-water, can be sources of infection. Since the vibrio is readily destroyed by drying, only freshly contaminated objects are dangerous. Yet it has been shown that the vibrio, when kept moist, may retain its vitality for a considerable time. (a) These organisms may find an abode in persons actually or apparently healthy. Thus, during the winter epidemic of 1892-93 the presence of Koch's vibrio was demonstrated, in the Hamburg Hygienic Institute, in twenty-eight healthy persons; and also in the case of certain families similar observations were made. These twenty-eight persons had been in contact with cholera patients, and their stools were solid or semi-solid. Abel and Claussen found vibrios in the faeces of 13 out of 17 healthy persons who had been in daily intercourse with cholera patients. (b) In the stools of convalescents from cholera vibrios were found after 50, 47, 27, 16, 10, and 8 days; and (c) it has been shown that they may remain alive and capable of proliferation in choleraic dejecta for as long as a month, but that, as a rule, they cannot be isolated after a few days. (d) In ordinary milk it survives 12 hours to 6 days, on fruit and fish for some days, the duration depending on the acidity of the media and the occurrence of other antagonistic saprophytes. (e) The vibrios are soon killed by drying, a few hours being sufficient if the layer of vibrios is thin. Here, again, the results are divergent according to the mode of conducting the experiment. (f) Even severe degrees of cold can be resisted, *e.g.* a temperature of  $-15^{\circ}\text{C}$  for not longer than 59 days (Brehme), while at  $-20^{\circ}\text{C}$  they do not survive beyond a maximum of 8 days (Abel). (g) Their resistance to acids depends upon various conditions. In pure water vibrios are killed by hydrochloric acid in 0.05 per cent solution in 6 minutes, while in the presence of pepsin, acid in 0.019 per cent solution is fatal. If, however, the fluids contain albumin or peptone, acid to the extent of 0.097-0.217 per cent is necessary, and the acid must act for 1 hour. By drinking 600 c.c. of water on a fasting stomach and siphoning off the contents in a quarter of an hour, a fluid with an acidity of 0.03 per cent HCl is obtained, which kills vibrios in 15 minutes. Vibrios are killed by an exposure to a temperature of  $56^{\circ}\text{C}$ . in about an hour; the exact temperature and duration of exposure necessary varying with the conditions of the experiment. (h) In water they remain alive for many days; in sterile distilled water, however, for only 24 hours, while in natural waters their life probably extends to weeks or months. Orgel, indeed, succeeded in keeping them alive in ordinary Elbe water for almost a year.



**Cholera Toxin.**—Experiments made with a view of determining whether cholera vibrios give rise to a soluble toxin have proved contradictory. Kolle and Wassermann, for instance, found that the filtrates of cultures one to five days old had no toxic action, but that cultures some months old afforded a toxin which resembled in action ptomaines but not that of a choleraic intoxication. On the other hand, Metchnikoff and Roux, by growing vibrios in collodion sacs in the peritoneal cavity of guinea-pigs and then on special media, stated that they procured a soluble toxin and, moreover, obtained also an antitoxin. These results have not, so far, been confirmed, and at the present time it is considered that the toxin, as we know it, is simply the intracellular toxin set free by the death and solution of the vibrio. It is chiefly through using this intracellular toxin that attempts have been made to give rise to immunising bactericidal serums in the blood of those inoculated. We need not here consider at length these various vaccines, because, though some are in actual use, yet they undoubtedly require much improvement before they can be considered to be of considerable therapeutic value.

**Immune Serums.**—*Haffkine's method* of protection consists in inoculation with two viruses. The attenuated virus was got by growing vibrios at 39° C. in bouillon, over which a constant current of air was passed. The powerful virus was obtained by frequent passage through the peritoneal cavity of guinea-pigs, and was termed the fixed virus. Inoculations are done in two stages. First, 0.1 to 0.5 c.c. of a 24-hour agar tube suspended in broth is injected subcutaneously. Secondly, three to eight days later, the same amount of the virulent culture is injected. The cultures may be previously sterilised by the addition of 0.5 per cent carbolic acid.

*Kid's Method.*—An agar culture of about 20 milligrammes of growth is suspended in 10 c.c. of salt solution, and sterilised for a few minutes at 50° C., to this 0.5 per cent carbolic acid solution is then added. The dose consists of 1 c.c. of the solution—equivalent to 2 milligrammes of culture. The bactericidal value of the patient's serum obtained by this method is 200 times as great as before treatment. Thus, while before inoculation 0.6 grammes of the patient's serum was necessary to protect guinea-pigs against ten times the fatal dose of vibrios, after inoculation only 0.003 was required. By this means, then, the patient's serum has acquired a bactericidal value of 3 milligrammes, while the protective action of the serum of a patient convalescent from cholera is only equal to 10 milligrammes, i.e. more than three times as weak.

*Strong's Method.*—Strong, starting from the hypothesis that in order to procure an immunising serum of high value it is necessary to have a solution containing as many free combining groups (receptors) of the vibriotic molecule as possible, devised methods by which this could be brought about. The cholera vibrios among other constituents have a peptonising ferment which is not killed by heating to 60° C. Strong found that by digesting at 37° cultures previously killed and known to possess good peptonising qualities, abundance of receptors were set free. The presence of these is shewn by their power of binding uniceptors

(agglutinins) and amboceptors (bacteriolysins) in a cholera immune serum. The actual method employed was to take large quantities of agar cultures, suspend them in salt solution, sterilise at  $60^{\circ}$  C., and then digest (autolysis) at  $37^{\circ}$  for 2-5 days. The solution is then filtered, and the filtrate used for procuring cholera immune serums. 3-4 c.c. of this vaccin inoculated into rabbits produced a serum with a bactericidal value of as high as 0.25 milligrammes, *i.e.* 12 times as powerful as that produced by Kolle's method. This vaccin has not as yet been sufficiently tried on man. In the case of Haffkine's and Kolle's vaccins and other modifications *e.g.* Murata's, good results are on record, and it is possible that really efficient vaccins may be obtained by some such method as that just described.

**Summary.**—If we now review shortly our position with regard to the bacterial etiology of cholera, we find that (1) vibrios of a particular kind are so constantly associated with the disease that their absence may justly be taken as an error in observation; (2) vibrios are frequently found in pure culture to the exclusion of other organisms; (3) none of the various cultural tests, taken singly, suffice to establish specificity of vibrio, but these, taken together with the reactions to a specific serum, make the nature of the isolated vibrio certain, and that such a vibrio is the cause of cholera there can hardly be any doubt at the present day.

We shall conclude this account with directions to guide the physician in the bacteriological diagnosis of cholera; but we must premise that, comparatively simple as this is in skilled hands, it cannot be undertaken by persons unfamiliar with bacteriological methods.

#### **Bacterial Investigation of Bowel-Contents and of Dejecta.**

1. A microscopic examination of fresh and stained specimens is advisable. For staining use dilute carbol-fuchsin (1 : 10  $H_2O$ ). An examination of the "rice" particles will often reveal vibrios in pure culture.

2. Inoculate a drop of peptone. Keep for half an hour at  $37^{\circ}$  C. Examine for vibrios. They may be detected when not originally seen. These are merely preliminary but useful tests, and recourse must be had to a systematic and thorough examination. Detection may be in some cases easy, in others difficult, so that all possible methods should be adopted; these, however, may be modified according to the results of microscopical examination.

3. *Gelatin Plates.*—Starting with a loopful of slimy matter, make dilutions and pour out two sets of three or four dilutions each. Incubate at  $22^{\circ}$  C. for 18 hours. Make impression specimens or examine suspicious colonies. Make sub-cultures on agar and peptone.

4. *Agar Plates.*—The agar is poured out into the plates and then dried—with the cover of the plate removed—at  $37^{\circ}$  C. for half an hour. A loopful of slime is stirred up in 5 c.c. of broth, and the surface of each plate is carefully smeared with a loopful of this fluid. Dry again the uncovered plates at  $37^{\circ}$  C. for half an hour, then incubate, and examine in 12 to 18 hours. By this means superficial isolated colonies can be got. Cholera colonies have by reflected light a peculiar transparency, but they cannot be distinguished from cholera-like colonies.

5. *Peptone "Enriching Method."*—This method, originally introduced by Schottelius, is by far the most important method of examination for vibrios, and should on no account be omitted. Inoculate six tubes containing each 10 c.c. of peptone with a loopful of material. In 6 to 12 hours examine the tubes, especially those with any pellicle formation. Make sub cultures into further peptone tubes, also gelatin and agar plates. Further, to 50 c.c. of peptone solution add 1 c.c. of faeces, and then proceed as before.

If by any of these methods a pure culture of vibrios has been isolated, the culture must now be tested with a view of determining whether it is **true cholera or not.**

*Preliminary Test.* This may also with advantage be used during the process of investigating suspicious colonies. A specific serum with an agglutinating value of about 1:10,000 for true cholera is necessary. This is diluted with 0.8 per cent salt solution to 1:500. A trace of the colony is now rubbed up in a drop of this dilution and incubated as a hanging drop at 37°. In twenty minutes at least agglomeration should be evident to the naked eye or low magnification. A control with normal serum in ten times the concentration should be negative. If there is no agglomeration in the hanging drop the colony is almost certainly not cholera.

*Quantitative Test.* This is applicable where the isolated or pure culture agrees in morphology, growth, etc., with true cholera. Dilutions of the specific cholera serum are made in strengths from 1:50 to 1:2000. (A) 1 c.c. of each dilution is taken and 1 loopful of culture rubbed up in each tube. (B) The same is done using a known cholera culture. (C) Further, a control is made using normal serum from the same species of animal as the specific serum, the concentration being ten times as great; to this is added the culture to be tested. (A) and (B) should agree, (C) if agglutination occurs at all it should only be in the very highest concentrations. With the results of this quantitative test Pfeiffer's phenomenon should now agree.

*Pfeiffer's Phenomenon.*—A specific serum must be used of the value of at least 0.0002 grammic. The following mixtures are then made. (A) 5 times the unit dose, i.e. 1 mgm. serum + 1 loop of suspected culture + 1 c.c. broth; (B) 10 times the unit dose, i.e. 2 mgm. of serum + 1 loop of culture + 1 c.c. broth; (C) 50 times the unit dose, i.e. 10 mgm. of normal serum + 1 loop culture + 1 c.c. broth; (D)  $\frac{1}{2}$  loop of culture only + 1 c.c. broth. These mixtures are injected respectively intraperitoneally into four guinea-pigs (200 grammes). If the culture is cholera, then (A) and (B) should show a positive reaction in 20 minutes, at latest 1 hour. (C) and (D) should give a negative reaction.

*Inoculation of a Suspected Water.*—To 10 flasks each of 100 c.c. of  $H_2O$ , add 10 c.c. of 10 per cent peptone solution, making the solution now contain 1 per cent peptone. Incubate at 37° C. Examine for pellicle formation, and proceed as before.

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## MORBID ANATOMY

The morbid changes disclosed by post mortem inspection of cholera cases vary with the stage of the disease at which death took place. As a general rule alterations in blood distribution are the most prominent feature of early deaths. Epithelial disorders of mucous tracts and evidences of glandular irritation occur later; and in more protracted cases, indications of more serious structural changes inflammatory or necrotic may be seen. The morbid anatomy of typical cholera is characteristic and constant. The surface of the body retains the peculiarities, shrivelling and lividity, manifested during life. Post mortem rigidity appears early and lasts long. In some cases muscular contractions occur soon after death and cause distortions of the body. Post mortem rise of temperature has also been observed.

The digestive tract reveals signs of grave disorder, which are usually most marked towards the termination of the ileum. The stomach is generally empty, its lining membrane is usually congested, the degree of hyperemia varying; ecchymoses are occasionally seen, and, rarely,

hemorrhage into the cavity; a state of catarrhal inflammation is sometimes found; the contents may be acid, neutral, or alkaline; the duodenum and jejunum usually exhibit hyperæmia, either continuous or patchy, arborescent or capillary. The lining membrane is generally swollen and sodden, and a pulpy material can be scraped off it, which consists mostly of granular cells and amorphous protoplasmic masses. Enlargement of Brunner's glands has been described (Griesinger), and exudation, often extensive, is frequently seen. Whether this shedding of epithelium be the result of a necrotic process during life or a post-mortem detachment is a subject of doubt and dispute. The ileum shews similar changes, but especially the last twelve or eighteen inches. The solitary glands are enlarged, and stand out prominently, and Peyer's patches are congested and swollen. This portion of the gut may also be covered with a croupous or diphtheritic pellicle, more or less adherent to the surface, and flocculent processes may project into the lumen of the tube, and may occasionally fill and obstruct it. Separation of this material may give rise to excoriation or even to ulceration. Ecchymoses of the walls and hæmorrhages into the cavity of the small intestine sometimes occur. The large intestine is generally less seriously diseased than the small. Congestion and catarrhal inflammation may occur, and in rare cases ulceration giving rise to hæmorrhage. The walls of the intestinal tube are generally thickened, and the lumen contracted. The peritoneal surface is injected, and presents, as Sir S. Wilks observed, a characteristic rosy colour. The peritoneal cavity contains no fluid. The mesenteric glands are enlarged, hyperæmic, and infiltrated with a whitish granular exudation (Aitken).

The *contents of the intestines* vary in quantity according to the amount of vomiting and purging during life; they vary in quality according to the stage and intensity of the disease. The cholera stool is a turbid, grey or greyish-white liquid, resembling water in which rice has been boiled. On standing, a granular, curdy, or flaky material subsides, leaving a whey-like supernatant fluid. The reaction of the material is alkaline, and its specific gravity from 1005 to 1015. The material found in the intestines after death resembles the sediment which settles from the evacuations passed during life. The solid elements in a motion amount to from 10 to 30 parts per 1000, the soluble salts from 5 to 10, and albumin and extractives from 2 to 20 (Parkes). The amount of albumin is small, but of salts—sodium and potassium chloride, sodium phosphate, carbonate, and sulphate—considerable. Nitric acid sometimes gives a red reaction. Considered as a derivative from the blood the cholera evacuation accounts for a large loss of water, a large loss of soluble salts, and a moderate loss of albumin and animal matter.

The *microscopy of the intestinal discharges and contents* has been the subject of laborious investigations. The objects found are embraced in the following categories:—

1. Débris of food.
2. Results of epithelial proliferation and glandular irritation—



amorphous, granular, and protoplasmic masses, granular cell forms, and cloudy epithelia. The amount of epithelial cells found in the contents after death exceeds that discovered in the stools during life.

3. Red blood-cells and leucocytes. Much of the protoplasmic granular material which forms so large a proportion of the solid constituent of the stool is held to be derived from changes which have taken place in white cells that have migrated from the blood (Lewis).

4. Organisms: some peculiar to cholera, others incidental to it. The bacteriology of the disease has been already described.

The *liver* is generally affected with venous congestion, the colour being dark, and venous blood escaping on section. The gall bladder is full of bile, which in later stages is thin and watery. Shredding of the epithelium of the bile-ducts has been described. There is no mechanical impediment to the discharge of bile through the ducts.

The *spleen* is not enlarged, on the contrary, it presents signs of contraction and expulsion of liquid.

The *kidneys* exhibit evidence of grave pathological disturbance. They are increased in size and much congested. Ecchymotic spots and patches are sometimes seen beneath the capsule and throughout the parenchyma. The tubes are blocked with a granular material. The epithelial cells are cloudy and swollen, and in later stages fatty. In advanced cases the tubes are devoid of epithelial covering. The cells undergo, in fact, an acute process of degeneration and destruction.

The state of the *urine* accords with these conditions. The excretion is at first suppressed, then scanty, of high specific gravity, albuminous, and containing casts—epithelial, granular and hyaline, and ultimately, in prolonged cases, abundant in quantity, watery, and devoid of albumen. The proportion of saline materials is greatly diminished in the urine of cholera, and of urea somewhat. Indican is a conspicuous constituent (Crombie). Bright's disease is a rare sequel of cholera. Temporary glycosuria is sometimes met with. The *bladder* is generally empty and firmly contracted in cases fatal early in the disease.

The *circulatory system and blood* undergo serious and characteristic changes. The heart is not altered in structure, but in some cases hemorrhagic spots and patches may be observed. The right cavities are generally distended with dark tarry blood; the left, as a rule, are empty. The distension extends into the venæ cavae, and into the pulmonary arteries as far as the lungs. In a considerable proportion of cases white clots are found in the right cavities, and extending into the pulmonary arteries: detached thrombi have also been found in the latter. Detachment of the epithelium of the vessels and adhesion of the blood to the denuded surface have been described (Thudichum). Dr. Wall concludes from clinical and post mortem observations that thrombosis is a common incident of the collapse stage of cholera, and that the clots in the heart and vessels undergo liquefaction, fragments of them sometimes remaining as pulmonary emboli and infarcts. The pulmonary veins are found empty and contracted in cases fatal during the stage of collapse. The



distribution of blood in the body is abnormal, the veins and their tributaries are distended with thick dark blood, and the arteries and capillaries empty. The solid organs exhibit well-marked venous engorgement. In the later (reactive) stages of the disease these conditions of the circulation undergo change; also when recourse has been had to warm saline intravenous injections—the change being towards a restoration of the ordinary distribution and balance of the blood.

The physical, chemical, and microscopic conditions of the blood have been made the subject of elaborate research. Three osmotic processes appear to exist during the progress of choleraic disease: 1st, an exosmotic effusion from the vessels into the intestinal canal; 2nd, an exosmotic current from the corpuscles into the surrounding fluid; and, 3rd, an endosmotic transit of fluid from the tissues into the vessels. By these processes the blood becomes profoundly altered physically and chemically. The outflow of constituents has been determined by Schmidt to take place in the following order: the water transudes before the solids of the serum, the inorganic before the organic solids, the chlorides before the phosphates, the salts of soda before the salts of potash; the alkalinity being much diminished. The same law applies to the other currents, which, however, are smaller and later, and fail to replace the material which has escaped. The blood in acute cholera is therefore found to be of high specific gravity, even 1073, very dark and inspissated, and deficient in water and salts. Cells and albumin are in excess, but authorities differ as to the amount of fibrin-factors and the coagulability of the blood. The amount of oxygen in the blood-cells is seriously diminished. The blood regains its brightness on exposure to air in thin layers, and on contact with the intestinal discharges (Parkes). Urea has been found in it in cases fatal in the algid stage.

Owing to concentration, due to severe purging and vomiting, there is an increase in the number of red blood-corpuscles or polycythæmia to between 6,500,000 and 7,500,000; with this there is a corresponding rise in the percentage of hæmoglobin. As originally pointed out by Virchow, and confirmed by Lewis and Cunningham, there is a leucocytosis. In moderately severe cases the count is about 30,000; before death a leucocytosis of 50,000 is not uncommon. In the algid stage a leucocytosis of 40,000 to 60,000 is of very bad prognosis (Biernacki). The leucocytosis is polymorphonuclear. No special organism or material of the nature of virus or toxin has been detected in the blood of cholera either by the microscope or by chemistry. For cholera toxin, *vide* p. 455.

The lungs in a case of death in the collapse stage are found to be light, dry, and shrunken. There is a deficiency both of blood in the vessels and of air in the alveoli. These are the characteristic cholera lungs; but in later stages they may be congested, œdematous, or collapsed. The pleuræ are usually healthy.

The brain and its membranes exhibit venous congestion. Signs of meningitis are sometimes present in advanced cases.

The tissues are dry, doughy, and shrunken from removal of water.

The muscles are also dry and contain an unusual amount of urea. They are sometimes found ruptured.

**Theory of Cholera.**—The phenomena observed during life and the appearances seen after death undoubtedly indicate that the choleraic process is due to the entry into the system of a poison which causes, in the first instance, violent functional disturbances; then sets up serious organic disorders, and finally gives rise, if life be prolonged, to important structural changes. The early incidents of cholera cases—more particularly the varying duration of the incubative stage, the usual occurrence, but occasional absence, of initial signs of intestinal irritation and nervous disturbance and depression—would suggest that the disease may be due either to ingestion of a poison elaborated elsewhere, in which case the invasion would be sudden, and the effects depend on the dose; or to the reception into the intestinal tube of a microbe in circumstances favourable for its multiplication; in the latter case symptoms of intestinal derangement, of longer or shorter duration, would precede the general poisoning by absorption of the elaborated product. (For cholera toxin, *vide* p. 455.)

The phenomena of cholera, especially of its later stages, constitute a remedial reaction; and the disease has with plausibility been likened to a febrile paroxysm with a severe and prolonged algid stage. Cases and outbreaks of malarial fever have been observed which it was found almost impossible to distinguish from cholera. On the other hand, in some cases and outbreaks of the latter disease the febrile phenomena assume a marked prominence. The poison seems to exercise a special influence—deleterious and destructive—on the epithelial elements of the intestinal and urinary tubes, and on the glands and follicles of the former: but a strong impression on the nervous system, leading to contraction of arterioles and disturbance of the balance of the circulation, with preponderance towards the venous side, is a very early effect of the poison in the blood, which soon undergoes important dynamical, organic, and chemical alterations. Many of the later incidents of cholera are due, no doubt, to absorption from the tubes and tissues of secondary poisons of bacterial or degenerative origin. The view that the intestinal disturbance is sufficient to account for all the other phenomena of cholera as secondary and consequential effects is no longer tenable; and the choleraic process cannot be satisfactorily explained otherwise than as the effect of one of those organic poisons which constitute a very early stage of decomposition of proteids, or result from the metabolism of these by the agency of micro-organisms.

When the virulence of the poison has been spent, or its removal effected, the primary disturbances set up by it are very soon and completely recovered from. The secondary changes occurring during the stage of reaction are more serious and prolonged; but these likewise very seldom leave permanent structural defects.

## CLINICAL ASPECTS OF CHOLERA

**Forms of Cholera.**—In different epidemics and different individuals these present considerable variation. It will be most convenient to describe, in the first place, the phenomena of an ordinary form of disease most frequently met with; and then briefly state those less common manifestations which are seen during the course of epidemic outbreaks, and seem to owe their exceptional character to variations in the strength and amount of the poison, or to peculiarities in the constitution and proclivities of individuals who have been subjected to its influence.

**Ordinary Form.**—In a characteristic case of cholera it is always possible to distinguish certain well-marked stages which have been designated by their most striking features. A premonitory or incubative stage can be recognised in a large proportion of cases, followed by the stage of evacuation, of which purging, vomiting, and muscular cramps are the most prominent phenomena; to this succeeds a stage of collapse, designated, as the name implies, by profound depression of all the functions of the body; finally, a stage of reaction, in which more or less improvement is manifested, ends, in favourable cases, in recovery.

**Stage of incubation** is that which intervenes between the reception of the poison and the manifestation of serious and characteristic disturbance of health. Its duration varies from a few hours to a few days, not exceeding ten. Three to six days appear, inferentially, to be the usual length of this stage; though precise and positive knowledge is wanting, owing to the lack of exact information as to what enters the system and how and when it effects an entrance. The symptoms of the premonitory stage of health which may be felt or observed during this period are usually confined to gastro-intestinal irritation, and to a disturbed or depressed condition of the nervous system. Diarrhœa is the most common premonitory symptom of cholera: it may last for hours or even days, and is apt to be attended by watery, motions being passed three or four times a day; it is usually painless or accompanied with griping. There is often a feeling of fullness or oppression at the pit of the stomach, and there is reason to believe that in this stage digestion is seriously impaired (Chevers). In some cases the premonitory symptoms take the form of malaise, depression of spirits, anxious expression, exhaustion, giddiness, tinnitus, and headache. In the most cases premonitory symptoms are not noticeable or are very slight, and the disease sets in without warning, with violent purging, vomiting, speedily followed by cramps and progressive exhaustion. The essential phenomena of the *stage of evacuation*, which may last from two to twelve hours or longer—the duration depending on dosage and vital resistance. The purging is frequent, copious, and watery. The earlier stools are feculent, the later pale, resembling rice-water in which rice has been boiled—a flocculent or curdy sediment being deposited on standing. Later motions are sometimes sanious.

Successive evacuations should be received in separate vessels for observation and comparison. There may be griping or abdominal pain; more frequently there is neither. The bulk of material passed in this stage is often very large. Vomiting generally begins later than purging: the contents of the stomach are first expelled; and it has been observed that these are often undigested, though they have been in the stomach for some time. The later rejections are watery and copious, emitted with force, and occasionally tinged with blood. Vomiting is easily excited by ingesta, and these are generally returned sooner or later. In some cases distressing and exhausting retching occurs without much result. The reaction of the vomited material varies; it is sometimes very acid. Muscular cramps are a painful feature of this stage; they may begin with the purging, and be prolonged into the next stage. The legs are their most frequent seat; but the muscles of the abdomen and back, and in some cases the whole muscular system, may be affected; the cramped muscles feel hard and knotty, and in many cases the pain is very severe. The temperature of the body falls somewhat as this stage proceeds, the surface becoming cold, dusky, clammy, or covered with sweat. The features are drawn, eyes sunk, expression anxious or blank, fingers and toes shrivelled, tongue white and cold. There is great thirst and much restlessness. The breathing is not thus far much affected, but the pulse rises in rate and loses in force. The patient becomes greatly exhausted, and, though generally sensible, is apathetic. Recovery may occur in this stage by cessation of purging, vomiting, and cramps, and with gradual restoration of strength; but in the majority of cases a more profound depression of vitality sooner or later supervenes. This is the *stage of collapse*, into which the patient may lapse gradually or suddenly. It may last from two or three to forty-eight hours, or even more, the attention being withdrawn from the evacuations, and arrested by the signs of alarming exhaustion. Liquid, colourless motions may still be occasionally passed involuntarily; or the presence of watery material may be detected in the intestines by palpation or succussion. Vomiting or attempts to vomit may persist, and cramps are often present, sometimes terribly painful. But these symptoms are overshadowed by the evidences of failing power: the pulse flickers and fails at the wrist, and is sometimes imperceptible in the brachial and almost so in the femoral arteries: its rate, always accelerated, may rise to 120 or 140, or even higher. The heart-sounds get less distinct, especially the first: in some cases murmurs and friction sounds are detected in this stage (Wall), which betoken disturbed and inco-ordinate contraction of its walls or the existence of clots in its cavities.

The capillary circulation becomes slow and feeble, the surface gets livid; respiration is quick and shallow; painful and often paroxysmal dyspnoea arises, compelling the sufferer to struggle for breath: the expired air is cold, and deficient in carbonic acid. The face presents the characteristic choleraic expression—features pinched, skin drawn, eye-balls sunken and surrounded by a dark areola, lids half-closed, pupils

contracted, mouth open, teeth covered with sordes, tongue cold, face apathetic. The general surface is cyanotic and clammy or bedewed with cold sweat, the fingers and toes are wrinkled. There is great restlessness and profound debility. The intelligence is clouded, the senses impaired, the muscular power diminished: in some cases sense and sensibility and capacity of movement are retained, in others coma or a semi-comatose state exists. The voice is husky and feeble, or the patient can speak only in faint whispers. Thirst is imperative, and a feeling of coldness is felt. The urine is suppressed; the bladder is generally emptied in the preceding stage, and no further accumulation of urine takes place. The temperature of the surface and mouth is greatly, and in fatal cases increasingly, depressed, and may fall below 90° F., the temperature of the axilla is higher, but below normal, readings of 95 to 97° F. being not uncommon in this stage; the rectal temperature may be slightly subnormal or normal, but in time it shews a tendency to rise above the normal.

In this stage a peculiar and characteristic odour may be detected in the breath and from the skin. The motions are devoid of smell unless they are retained, in which case they quickly become offensive. It is in this stage of cholera that death most frequently occurs, and the fatal event may happen early or late, very suddenly or after some lingering hours while life and function are slowly waning. Death may occur from respiratory failure, asthenia, or coma.

The *stage of reaction* is, generally speaking, characterised by a gradual restoration of power and resumption of function. The pulse returns to the wrist, feebly and fitfully at first, but there is, in favourable cases, a progression in steadiness and strength. The breathing becomes easy and the patient tranquil. Blueness, coldness, shrinking, and clamminess of the skin give way to roundness and warmth. Temperature is normal or slightly raised. The stomach regains its tone, and food is retained. The stools resume their proper colour, some looseness may persist, but the motions are less frequent and less watery, and exhibit successively deepening tints of grey and brown. Urine is passed, though its reappearance may be delayed for many hours; it is at first watery, high coloured, of strong smell, high specific gravity, albuminous, and containing indican and casts; then it becomes copious. Mental activity and muscular power return, and complete recovery may take place within a few days.

So happy a result is, however, by no means invariable. In a considerable proportion of cases (from 10 to 25 per cent) events occur during the stage of reaction which constitute a serious departure from the normal sequence, and prolong the illness or cause death.

The variations which take place in the symptoms and course of cholera are numerous and well marked, and have led to the distinction of several forms of the disease. These varieties are apt to present themselves more or less prominently in different epidemics and at different periods of the same epidemic, and, for purposes of diagnosis and treat

ment, it is highly important to take them into account. They are best described in the order of succession of the phases of the ordinary disease.

1. The disturbance of health may be slight and transient. During an epidemic of cholera many persons complain of slight malaise, anorexia and looseness of bowels which pass off with or without treatment. This is the so-called *ambulatory* form. The disease appears to be arrested or abortive in the incubative stage. It is important to note that the comma bacillus is found in the stools of such cases, which may therefore be sources of infection.

2. In other and more frequent cases the diarrhoea is more pronounced and persistent—painless, accompanied, perhaps, with nausea or vomiting, and sometimes with cramps. The stools are copious and watery, inclining gradually to the rice-water type. There is no suppression of urine. Cases of this kind occur in anticipation of or during an epidemic, and contribute to that excessive prevalence of diarrhoea which statistics indicate as generally concomitant with cholera. With or without the aid of medicine recovery usually takes place within twenty-four hours; but not unfrequently such cases, especially if untreated, lapse into true cholera. This form of disease has received the name of *choleraic diarrhoea* or *cholera*, and appears to represent an arrest in the stage of evacuation.

3. On the other hand, this stage may seem to be absent, patients passing quietly into fatal collapse without either vomiting or purging. Cases of this sort have been described as occurring at Karachi in the year 1846, and at Teheran in the same year. On post-mortem examination, however, the characteristic lesions and evacuations of cholera are found in such cases. The absence of evacuation and the rapid prostration have been attributed to the large dose or special virulence of the poison which rapidly overpowers vital resistance and energy. This form, which is very rare, has been called *cholera sicca*.

4. The stage of collapse is very short; death takes place suddenly from respiratory failure, with symptoms of gravely disturbed cardiac action and impeded circulation through the lungs. This may depend on spasm of the pulmonary arterioles, on the difficulty of transmission of the inspissated blood from the right heart into the lungs, or on the formation of clots in the right cavities. Dr. Wall described murmurs and friction sounds which he attributed to this cause: the condition, though frequently, is not necessarily fatal. It may be called the *embolic* form or phase of cholera.

5. On the other hand, the cold stage may be prolonged up to thirty-six or forty-eight hours. Recovery sometimes takes place in such cases but the unfavourable contingencies of the reaction stage are more likely to occur in these circumstances.

6. The intelligence of the patient is in some cases marvellously keen during the stages of evacuation and collapse; but a condition of growing prostration and apathy is the rule. In some instances the clouding of the intellect and dulling of the senses are early and profound, and out of



harmony with the other symptoms. This *primary choleraic stupor* has been attributed to the direct effects of the choleraic poison on the nervous tissues (Wall).

The varieties of cholera depending upon variations in the phenomena and course of events in the stage of reaction are numerous and important.

7. The *reaction may be imperfect*. Some revival from collapse may occur, but the temperature remains subnormal, purging and vomiting continue, the pulse does not regain power, exhaustion is progressive, and the patient in time sinks from asthenia, or may pass into a fatal "typhoid" phase.

8. In other cases, after temporary amelioration, there is a *relapse* of the purging or vomiting, and death by exhaustion sooner or later ensues, though recovery from the relapse is possible. The relapse may be induced by the use of purgatives or indiscretion in diet.

9. A very serious variety of cholera is the *hyperthermic form*, in which during collapse the rectal temperature is found rising to 100° F. and over. The axillary temperature soon follows suit, and a very high degree of heat (as much as 107° F. in the axilla, and 109° F. in the rectum—Wall) may be reached. Such cases are very fatal.

10. During the stage of reaction patients not unfrequently lapse into a *typhoid state*. This does not depend on excessive temperature or on suppression of urine, but seems to correspond rather with the state of "prostration with excitement" met with in other circumstances. The symptoms are those of the typhoid condition, however caused—moderate elevation of temperature (101° to 102° F.), excitement of pulse and respiration, failing power, restlessness, delirium, subsultus, dry tongue and lips, sordes, stupor merging into coma, and in prolonged cases purpura and bed-sores. This condition is generally, but not necessarily fatal. Convalescence is very slow in the non-fatal cases. There are cases which seem to occupy an intermediate position between the hyperthermic and the typhoid cases; in these mild fever of an intermittent or remittent form complicates and delays recovery.

11. In these febrile states *eruptions* sometimes make their appearance. The more common are urticaria and erythema: the latter may be bright in colour and widely diffused. Roseola, maculæ, and bullæ have been described. The eruption in such cases may perhaps be considered a sort of exanthem.

12. Suppression of urine, and the consequent *uræmia*, constitute the most important and anxious feature of an abnormal reaction. The re-appearance of urine is sometimes delayed for many hours or even days without serious results; but such a delay is always a cause of anxiety, and in most cases of prolonged suppression cerebral symptoms attest the retention of waste matters in the blood. Stupor with restlessness, muttering delirium, spasmodic contraction of muscles, bloodshot eyes, contracted pupils, dry lips and tongue, sordes, vomiting, slow pulse are the chief symptoms; the patient often relapsing into fatal coma. The bowels may remain relaxed; this is favourable and should not be checked.

Vomiting of grass-green material has been noted in this state. The secretion or discharge of bile may be suspended, and this adds to the gravity of the case. Chevers has described this dual suppression as cholo-uræmia. On the re-establishment of the urinary excretion the alarming symptoms may subside, and convalescence proceed.

**Sequels.**—A number of untoward events may arise during the stage of convalescence; they may be classified as follows:—

1. *Functional.*—Under this head are included anæmia, debility, nervous depression, jaundice (a rare but dangerous complication), gastric irritability, persistent hiccup, insomnia, dementia, paraplegia, anasarca, irregularity of bowels and chronic diarrhœa. In pregnant women abortion is almost invariable; the child dies during the algid stage and is sooner or later expelled. Signs of cholera are often found in the fœtus (Wall).

2. *Inflammatory.*—(Edema of the lungs, bronchitis, pneumonia, and pleurisy are not unfrequently met with, especially in conjunction with suppression of urine. Meningitis, conjunctivitis, arthritis, and parotitis have also been described. The parotid inflammation sometimes ends in abscess. Dysentery is an occasional complication of convalescence, but it is mild and amenable to treatment. Dropsy has been described as a result of consecutive nephritis.

*Destructive.*—Ulceration of the cornea is not uncommon. Bed-sores sometimes form in cases of low typhoid character and of uræmia, if the nursing be defective. Gangrene of the nose, ears, penis, and scrotum, more rarely of the fingers and toes, are also met with, especially among natives of India. The dead parts, if limited, may be separated and cut off, but extensive gangrene is generally fatal.

**Diagnosis.**—The maladies which most closely resemble cholera are ptomaine poisoning; mushroom poisoning; certain varieties of diarrhea; and some rare malarial fevers, with intestinal complications and a profound and prolonged algid stage. The identification of Asiatic cholera turns upon clinical, epidemic, and bacteriological considerations. The clinical features which mark an ordinary case of cholera are: the copious, painless passage of watery motions, devoid of bile colouring, resembling rice water and exhaling a characteristic odour; the profound nausea and frequent vomiting of watery material; the suppression of urine; the muscular cramps; the cyanosis and shrinking of skin; the cold breath and whispering husky voice; the dyspnoea and restlessness; the prostration, torpor, and failing pulse; the cold sweats and depression of the surface temperature, with a tendency to rise of internal temperature. These constitute a group of symptoms which may be imitated, but are seldom if ever identical with those of any other flux. If cholera is known to prevail in the locality or neighbourhood, or circumstances permitting or favouring importation exist, suspicion naturally attaches to all bowel complaints, even if they do not present the extreme form just pictured. Similarly, cases of diarrhœa, however mild, arising in the midst of an epidemic of cholera are viewed with apprehension. If numerous seizures

occur in groups, and the mortality equals or exceeds 50 per cent, the identification is rendered more easy and certain. Cases of ptomaine and muscarine poisoning, which most resemble cholera, generally occur singly, or in small groups, and usually follow the eating of fish, shell-fish, tinned provisions, or mushrooms; fragments of mushrooms may be found in the stools. The association with prevalent malarial fever, the absence of epidemic cholera in the place or vicinity, the periodicity, the better marked febrile stage, the lower mortality, and the amenability to quinine, serve to distinguish the cases of malarial fever which, in the algid stage, may assume a choleraic character (*vide* p. 260). The suppression of bile and urine, the cyanosis, cramps, collapse and cold, and the high mortality are the chief circumstances which distinguish cholera from other diarrhoea. The bacteriological conditions are also important. The detection of Koch's vibrio in the evacuations constitutes, according to our present knowledge, a means of separating cholera from every other disease. The negative, however, is not true. In a certain, though small, proportion of cases the vibrio cannot be found. The application of the serum test may be resorted to in doubtful cases; but is seldom necessary. (*Vide* p. 457.)

**Prognosis.** The death rate of cholera varies with the character of the epidemic and the period of the outbreak. Fifty per cent may be accepted as an average death-rate, but it is often exceeded in specially severe outbreaks, and in the early stage of any outbreak. The very young and very old succumb more readily than the middle-aged; sucklings are seldom attacked. Women are rather less frequently seized than men; pregnancy is a dangerous complication. Organic disease of the kidneys is a specially unfavourable condition, and organic disease of the liver almost equally so. Drunkards are bad subjects; so are persons of feeble and damaged constitution; ill-health, however caused, is an unfavourable introduction to the choleraic struggle. During the progress of a case signs of good or evil omen are observable at every step.

**Bad signs**, in the order of the stages, are—sudden seizure, early prostration, early stupor, quick advent of collapse, restlessness, and fighting for breath, failing pulse, great depression of temperature, prolonged cold stage, hyperpyrexia, severe abdominal pain, blood in vomit and stools, persistent suppression of bile and urine, permanent muscular contractions, jaundice, lung complications, recurrent purging and vomiting, delayed restoration of body heat, "typhoid" symptoms, and indications of uræmia or cholo-uræmia, insomnia, and delirium.

**Good signs** are—maintenance of pulse during collapse, moderate depression of temperature, early and not excessive reaction, return of colour in the motions, cessation of cramps, restoration of urinary excretion, resumption of warmth and dryness of skin and normal colour and plumpness of face, quiet breathing, tranquillity, sleep.

The violence of vomiting and purging in the early stages are not necessarily indicative of a severe seizure, but their persistence is apt to result in delayed convalescence or fatal exhaustion.

**Treatment.**—Since about one-half of those attacked with cholera recover, with or without treatment, it is clear that processes antagonistic to the poison and curative of its effects arise within the organism, and are effective in that proportion of cases. What the precise nature of these processes may be it is impossible, in the present state of science, to affirm. Whether the poison of cholera lose its power by lapse of time, or be diluted, eliminated, or destroyed; or whether there be formed in the tissues or blood or intestinal tube some antagonistic principle—an alexin or antitoxin—we know not: in our ignorance of the process of natural cure it is impossible to formulate a rational system of treatment in imitation and furtherance thereof. Two principles may, however, be confidently stated, namely, (1) that it is obviously irrational and improper unduly to interfere with or thwart processes, which, though apparently morbid and injurious, result, as a matter of fact, in restoration to health in a moiety of seizures; and (2) that, in estimating the value of any system or method of cure, the law of natural and unaided recovery must be taken into account, allowing for the character and period of the outbreak.

**Prevention.**—The sanitary measures by which a community may be protected from cholera, by which its entry may be prevented, its spread controlled, its incidence and mortality minimised, are indicated by the facts and considerations adduced in the sections relating to the history, etiology, and epidemiology of the disease.

*Personal prophylaxis*, however, constitutes an important item of the treatment of cholera as affecting individuals. Certain circumstances and conditions have been recognised as rendering persons specially liable to attack. The chief of these are—bodily fatigue, mental worry, panic, disorder of stomach caused by consumption of raw fruits and vegetables (melons, cucumbers, and the like have been specially blamed), decomposing animal food, particularly fish and shell fish, excessive use of alcohol, drinking impure water or milk, the use of purgative medicines especially salines, exposure to cold, and, generally, anything tending to depress the general vigour and derange health. The conduct and regimen necessary to avoid these risks need not be detailed.

On grounds of reason and experience the most efficient preventive of cholera, both for individuals and bodies of men, is avoidance of infected localities, or, if practicable, removal to another place, higher and drier, where the disease is not prevalent. New-comers to infected places are specially prone to attack. Although the disease does not appear to be often, if ever, communicated directly from person to person, avoidance of association with the sick is advisable, because such association may involve exposure to the morbid conditions surrounding the sick.

Chemical disinfection of excreta and discharges, and of articles which have been soiled thereby, is obviously advisable; and the free use of such agents as carbolic and sulphurous acids highly commendable. Protection against attack by the administration of drugs, such as quinine and the mineral acids, has been tried without satisfactory results. The pro-

phylactic and perhaps curative use of acids is indicated by their inhibitory effect on the growth and multiplication of vibrios.

*Anticholeraic Vaccination.*—Various attempts have been made to render the system immune to choleraic infection by the injection of vaccins. The most widely tried is the method devised by Haffkine. He gave two injections of a weak and a strong vaccin, with an interval of five days between; the weak vaccin was given first to obviate the necrotic effect of the strong vaccin at the point of injection. Haffkine, however, has since used virulent cultures for the first injection without bad effects. Extensive inoculations of human subjects have been carried out by Haffkine in India. Many thousand persons have been vaccinated without accident or harm. Evidence has been gained that recent inoculations are protective; the incidence of the disease is reduced, but not the case-mortality. The effect of these injections appears, therefore, to be antimicrobial rather than antitoxic. No reliable curative serum has as yet been manufactured, though experiments indicate the probability of such being eventually discovered (*vide Immune Serums*, p. 455).

*Medicinal Treatment, Nursing, and Isolation.* The drugs and compounds which have been administered empirically in cases of cholera are legion. It is safe to assert that not one of them has established a claim to cure the disease. It were useless, therefore, to catalogue or discuss them. Four plans of treatment stand out prominently among others as possessing some basis of reason, and offering some promise of success; namely, the astringent, the eliminative, the antiseptic, and the stimulant. To these may be added the antispasmodic and the counter-irritative. The astringent plan contemplates the choleraic process as a hypercatharsis, and its danger as depletion; rice-water evacuations being regarded as potentially hemorrhage (Chevers). Astringents, mineral and vegetable, in combination with opium, antispasmodics, and stimulants, have, in accordance with this view, been administered by mouth and rectum, in the hope that if the dangerous flux be checked, the margin of recuperative power thus saved will suffice to avert fatal exhaustion and to restore health. It is possible, however, that the results thus to be prevented or cut short—the tremendous drain of serum, corpuscles, and salts from the veins into the intestinal tube, the reversal of the normal currents, and the abeyance of absorption—may have a salutary purpose, and within limits a curative function; it is doubtful whether the checking of these discharges is, as a dominant principle, a sound basis of action. Still the principle has its place in that scheme of treatment which, as we shall presently shew, experience has sanctioned.

The eliminative plan, on the other hand, looks upon the flux as adjunct as a means of conveying the cholera poison out of the system—and seeks to aid it by administering purgatives. But, apart from the well-established fact that purgation is of itself exhausting, especially so in the early stages of cholera when it ought to be most effective and beneficial, it is questionable whether it is wise to remove materials artificially from the intestinal tube—such, perhaps, as leucocytes or



their alexins, or innocuous bacteria—which may tend to neutralise or destroy the poison of cholera. As a matter of fact, Sir George Johnson's castor-oil treatment has been extensively tried and found wanting. Stimulation of the kidneys by diuretics has also been tried under the guidance of this hypothesis, and found to do more harm than good.

The antiseptic plan aims at neutralising the poison in the intestinal tube, or setting up conditions there which may render its elaboration impossible. Acids and germicides of many kinds have been administered with this object; but this plan may simply result in adding poison to poison, or irritant to irritant; in hindering a process of salutary decomposition, or in destroying the leucocytes or innocuous organisms and their products which may be doing good work. Practically, the plan has failed to cure cholera.

The stimulant or restorative plan simply endeavours to avert death from exhaustion, and to sustain the flagging vital powers in circumstances of terrible depression. Alcohol, ammonia, strychnine, and ether administered by mouth or rectum, or hypodermically, are the favourite remedies of this class, supplemented by strong soups and nutrient enemata. Even this method is not without its drawbacks. Gastro-intestinal irritation may be increased, mischief may arise during the reactive stage, or perhaps undue disturbance of the collapse stage may be hurtful. These considerations suggest caution in the use of stimulants.

The antispasmodic plan is based on the observation that the muscles of the intestines, arterioles, bile-ducts, limbs, and trunk are thrown by the action of the poison into violent contraction; pain and exhaustion tending to death are thus caused. The clamping of the pulmonary arterioles, impeding the circulation and banking back the blood—hindering, that is, its aeration in the lungs, the nutrition of the brain, the action of the kidneys and skin, and promoting flux—is considered specially perilous. Warm baths, chloroform inhalation, sedative and antispasmodic drugs, nitrite of amyl and nitro-glycerin, and warm intravenous injections, have been given to relieve spasm. This treatment has proved useful as a means of relieving some symptoms.

The use of counter-irritants is intended to remove morbid action from within to the surface, where it may be less hurtful and more under control. Measures of this kind may be useful as auxiliaries.

It may be asserted with confidence that in the present state of our knowledge no single principle or plan of treating cholera has met with much success. It is possible, nevertheless, to lay down certain rules of action which, as experience has taught us, may aid the patients in undergoing the terrible struggle for life which the choleraic process entails. These will be briefly stated as they apply to successive stages of the disease.

1. *Check the Preliminary Diarrhœa.*—All authorities are agreed as to the advantage of this measure, which promptly cures mild cases and prevents others from becoming dangerous. Combinations of opium with astringents and antispasmodics constitute the favourite formula.



y may be given in pill or mixture. The "cholera pill" ofists of opium, asafetida, and black pepper. Goodeve used lead and opium. Chevers preferred vegetable astringents. a tinctures, which have often proved so serviceable, are generally of laudanum or liquor opii sedativus with catechu or kino, com-cture of lavender or cardamoms, and spirit of chloroform. e, with or without brandy, according to the state of the an admirable remedy of similar composition, fulfilling the same dose and frequency of repetition must depend on the age and of the patient, the degree of irritability of the stomach, and of the remedy. The practitioner must exercise a careful and judgment on these points; it is inexpedient to lay ise rules or formulæ. If the stomach be very irritable a ultice or chloroform should be applied to the epigastrium, and ce given to suck. If medicines are still rejected the hypo-ction of morphine may be resorted to. It must be clearly l that the treatment now recommended is applicable to the y and evaculatory stages only. When collapse has fairly set nd astringents must be stopped; for absorption being now in hey are useless, and in the stage of reaction, when absorption in, they may do harm.

*maintain Physical and Physiological Rest.*—The patient must be d and the evacuations received in a bed-pan. Fussy changing and bedding must be avoided. Violent rubbing, rough lifting and other beds, transfer to another room or house, and, above ey are dangerous. Medicines, food, and stimulants should not n an irritable stomach; they provoke vomiting, excite irritation, se exhaustion. The indication is to refrain from anything that o the wearing effect of a most weakening malady.

*lore a Failing Circulation.*—If the pulse be maintained in the ie less done the better. If the pulse gradually lose volume and l become feeble and thready, a mild stimulant should be given mpagne and soda-water, weak brandy and water (iced)—in ls, or ammonia or spirit of chloroform well diluted. Should respond, nothing further is needed. If, however, the pulse perceptible at the wrist, and hardly perceptible in the brachial al trunks—if, at the same time, cyanosis and dyspnœa are well he condition is one of imminent danger. Hypodermic injec-ther, or cautious doses of nitrite of amyl or nitro-glycerin, up by champagne or brandy, may restore the pulse; but fects this so speedily and surely as the intravenous injection aline solutions. Sixty grains of sodium chloride and 30 of bonate are dissolved in one litre (about 35 ounces) of distilled he fluid should be sterilised by boiling, and injected slowly at ure of about 98.4° F., with strict antiseptic precautions, into veins of the arm, or into the subcutaneous tissues. A reservoir five or six litres should be kept ready and placed on a stand

about four feet above the level of the patient's head. The injection flows by gravitation through a flexible tube, by pressure on which the rate of flow is regulated. The rate of entry should be slow, say one litre in twelve minutes. The amount injected will depend on the effect; one to three litres may be required in different cases to restore the pulse (Wall). In most cases the fluid leaves the blood-vessels and passes into the intestinal tube, and the symptoms of collapse recur. They may nevertheless be removed again and again by a repetition of the injection and in some cases a permanent cure results. Experience has, however, shown that the proportion of recoveries has not been materially increased by the use of saline injections. Still, distress is for the time relieved, life is undoubtedly prolonged, some cases seem to be saved; and in the face of impending death anything that offers the faintest hope of rescue is justifiable. Dr. Cox of Shanghai has practised and advocated the continuous, slow intravenous injection of saline solution. The injection is made by gravitation from a vessel raised about two and a half feet, and maintained until the symptoms of collapse have finally disappeared, and reaction has been established. Intravenous injection of milk and transfusion of blood have been tried without much benefit, if any. It has been sought to restore fluid to the blood by injecting saline fluids and plain water into the cellular tissue, peritoneum, bladder, and rectum. No harm has resulted from such procedures, and little if any good. The fluid is readily absorbed, but as readily passes away through the intestines. It is possible that these artificial means of restoring water and salts to the blood simply keep the exosmotic current flowing, which might otherwise cease or be reversed through the altered specific gravity of the blood. It has also been sought to remedy stagnation of the circulation by the warm bath and mild rubbing of the limbs. These measures should be applied with the utmost gentleness. Rubbing with dry powdered ginger is a routine practice in India; clamminess and moisture of skin are to be removed, and mild stimulation of the cutaneous vessels and nerves attained. The practice, if cautiously followed, does no harm, and probably does some good.

4. *Conserve the Bodily Heat.*—The great depression of surface temperature which takes place in the collapse stage of cholera is no doubt due to many causes—amongst them the direct effect of the poison on the nerve centres, the disturbance of circulation, and the loss of fluids from the intestinal and cutaneous surfaces. It is probably more a sign than a cause of exhaustion. Still, it seems desirable to prevent the escape of the bodily heat. The temperature of the room should not be allowed to fall below 70° F., and the air in the immediate vicinity of the patient should be warmed by a few hot bricks or bottles—this is better than loading him with bedding. Ventilation should be free, but draughts avoided; in hot climates the punkah should be gently pulled. The surface should be kept as dry as possible, and gentle wiping with soft cloths or rubbing with dry ginger powder resorted to. The warm bath also tends to restore the surface temperature.

*Allay Thirst.*—The craving for fluids in cholera is astonishing, ought to be gratified; but large draughts excite violent vomiting, and lead to exhaustion. Giving lumps of ice to suck is perhaps the best method of quenching thirst; still, small quantities of iced soda-water, champagne and soda, barley or arrowroot water, milk and soda, or confuls of cold jelly or clear soup may be administered at short intervals. The injection of fluids into cavities and tissues tends indirectly to fulfil the same indication.

*Relieve Distress and Pain.*—The cramps undoubtedly constitute the painful symptom of cholera, and it is not easy to relieve them. Usually the opiates administered in the early stages exercise an anæsthetic effect. Hot applications, the warm bath, gentle frictions with various liniments, or even moderate counter-irritation with chloroform, nitro-glycerine, or mustard, may be tried; but nothing relieves cramps so effectually as moderate and intermittent chloroform inhalation. Camphor has been recommended internally, externally, and hypodermically. For severe abdominal pains which are sometimes met with, hot applications and counter-irritation with chloroform or mustard give relief. In the later stages a moderate dose of liquid extract of opium may be injected into the seat of pain. The relief of general distress is best accomplished by warm baths and intravenous injections, but these must be used with caution and judgment. Sir Lauder Brunton has recommended the subcutaneous injection of atropine in cholera, but rather on the ground of its known antagonism to muscarine, which causes symptoms closely resembling cholera, than on account of its anodyne properties. Sufficient trial has not as yet been made of the drug to warrant its confident recommendation.

*Check Persistent Diarrhœa.*—Persistent or recurrent purging, causing exhaustion and delaying recovery, sometimes occurs in the stage of reaction. Vegetable astringents or mineral acids may be given in small doses, well diluted, but the large, warm, astringent rectal injections recommended by Catani are more efficient. Twenty grammes (308 grains) of tannic acid and as much gum-arabic are dissolved in one litre of water. The injection is made very slowly by gravitation to such a depth as the patient can comfortably bear. Blood heat is the best temperature, and the material should be retained as long as possible (Wall).

*Check Irritability of Stomach.*—This may be manifested as obstinate vomiting or incessant hiccup; or signs of severe gastritis, induced perhaps by injudicious administration of food and stimulants, may be present. There is no special cure for this condition, which is to be treated on ordinary principles.

*Reduce Excessive Temperature.*—It is extremely difficult to fulfil this indication; and this is the more to be regretted inasmuch as the pyretic form of cholera is very fatal. Ice sucking and the slow administration of bulky cold enemata may be tried; antipyretics should be given. Tepid baths gradually cooled may be resorted to, but great caution is necessary in any such adventures.

10. *Restore the Secretion of Bile and Urine.*—As regards the bile, very little if anything can be done to promote its secretion or evacuation; in most cases, fortunately, nothing need be done. Usually, when the cold stage has passed and spasmodic closure of the ducts is relaxed, the flow is resumed. Sometimes the outpouring of the imprisoned bile is excessive and gives rise to bilious vomiting. In those cases in which the function of the liver has been so much impaired that a watery material is poured into the ducts instead of bile, no means have been discovered of correcting the condition. Calomel has been given in large and small doses, with the intention of stimulating the secretion and discharge of bile. Large doses are undoubtedly injurious, and small doses, even when combined with soda, are of very doubtful value.

The restoration of the urinary excretion is a more important object; its prolonged suppression is fatal. Dry cupping, hot fomentations and poultices may be applied in cases of delayed return; and water, milk and water, barley water, freely given. Diuretics should be avoided. When head symptoms are severe and the bowels confined, mild enemas, or even a little castor-oil emulsion, may be given; but great caution is necessary in the use of such measures. The bladder should be examined by catheter occasionally if necessary.

*Special symptoms, complications, and sequels* are treated according to the appropriate methods, always bearing in mind the great strain to which the system has been subjected by the choleraic process, the special danger of re-exciting gastro-intestinal irritation, or of putting additional stress on the damaged liver and kidneys, on the restoration of which to healthy function life so greatly depends.

In most cases of recovery from cholera health and strength are rapidly regained, and the patient in a few days seems none the worse for his attack. In some cases anæmia, emaciation, debility, deranged stomach and bowels, and general enfeeblement and bad health of a persistent and intractable description, ensue. Change of air is the best means of combating this state. Tonics and careful dieting and regimen are also necessary.

The *dieting* of cholera subjects is a difficult task. The simplest possible liquid food should be given in small quantities during the attack, and ordinary food be very gradually resumed during convalescence. It is needless to catalogue here the articles of diet which may be administered. These directions must be left to the discretion of the practitioner, but fatal relapses have not infrequently been caused by injudicious dieting. Finally, it may be asserted with confidence that, although no "cure" of cholera has as yet been discovered, careful attention to the state of the patient, with a view to the fulfilment of the needs which I have indicated above, will relieve much suffering and save many lives.

KENNETH MACLEOD

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K. M.

## DYSENTERY

(I.) BACILLARY. (II.) AMŒBIC. (III.) OTHER PROTOZOAN FORMS

## I.—BACILLARY DYSENTERY

By ANDREW DAVIDSON, M.D., F.R.C.P. Ed

Bacteriology and Pathology, by SIMON FLEXNER, M.D.

**SYNONYMS.**—Gr. *δυσέρεια* (δυσ, difficulty, *έρεια*, the bowel) Lat. *Tormenta*, Eng. *The bloody flux*; Fr. *Dysenterie*, *Trouble*, It. *Dysenteria*, *Flusso*, Span. *Dysenteria*, *Camaros de Sangre*, Ger. *Ruhr*, Swed. *Ricksol*.

**Definition.**—Dysentery is the clinical expression for a group of congestive or inflammatory diseases of the large intestine, often terminating in necrosis, ulceration, or gangrene; characterised by frequent mucous or serous stools, mixed with blood, and generally accompanied by more or less tormina and tenesmus, with or without fever.

**Forms of the Disease.**—Recent researches justify us in recognising



two specific forms of dysentery—the bacterial and amoebic—differing in cause, course, lesions, symptoms, and complications, as well as in their geographical range and mode of spread. Symptoms, clinically indistinguishable from specific bacterial dysentery, also arise from chol, dietetic errors, and mechanical, toxic, or parasitic irritants. Cases of this kind may be distinguished as pseudo-dysentery. Amoebic dysentery is described on p. 527.

**Epidemic Manifestations.** Dysentery occurs as an epidemic, endemic, and sporadic disease. Epidemics of dysentery may be divided into major, minor, and institutional, according to their extent of diffusion. Major or general epidemics occur only at considerable intervals, and last for three or four years, or longer, during which time they invade areas corresponding, say, to the half of Europe. They make their appearance almost simultaneously in widely separated localities, which are often marshy. From these primary centres the infection extends to neighbouring villages and towns, then to more distant places; but in such a manner that it passes over certain localities to attack others more remote, coming back later upon some of those spared at first, shewing that local conditions count for something in its diffusion. The disease dies out in winter, but reappears in the succeeding summers, and extends to countries which escaped during the first years of the outbreak. These general epidemics almost invariably begin in years of exceptional heat and drought, but they may persist and spread after the character of the seasons which started them have changed. As examples of this kind, we may mention the great European epidemics of 1538-40, of 1717-9, of 1779-83, and of 1834-36. These major epidemics are not to be confounded with the widespread outbreaks of dysentery following on war and famine, to which we shall presently advert. Apart from famine I have met with no accounts of major epidemics of dysentery in tropical countries. Minor or local epidemics are of frequent occurrence in most countries of Europe, but have been almost unknown in the British Isles except as asylum outbreaks, for more than half a century. In 1905 a small outbreak occurred at Aldershot, believed to have been introduced from South Africa; there were 170 cases and 38 deaths in a population of 31,000. Scarcely a year passes without epidemics of this kind being reported from France, Germany, Austria, Italy, and Russia, and they are also met with in tropical and subtropical countries. They are generally limited to areas corresponding to two or three townships or parishes, to one or two hamlets, and occasionally even to isolated houses. In certain years the number of these local outbreaks occurring in different parts of a country are so considerable as to approach the dimensions of a general epidemic, and when this is the case, the same meteorological conditions which determine the latter, viz. heat and drought, are generally in operation.

Institutional epidemics—caused in most cases, as are the other forms, by the specific bacillus—are confined to bodies of people living under the same conditions, as in barracks, camps, asylums, and jails. Their modes



spread are not always the same. The asylum dysentery of England does not appear, from Dr. Gemmel's statistics, to be a seasonal disease; whereas the dysentery of barracks and camps is generally most prevalent if not restricted to, summer and autumn.

**Endemic dysentery** is met with in warm climates only, where it occurs throughout the year in certain localities with more or less marked seasonal variations in frequency. No connexion between the cases can usually be traced, and it is exceptional for several members of a household to be attacked in succession.

**Sporadic dysentery** occurs in strictly isolated cases, in places and times where the epidemic or endemic forms are rare or unknown. This form is of special interest as bearing on the existence of the bacillus in the surroundings of man. A case occurring in England with *B. dysenteriae* in the stools has recently been described by Dr. Saundby.

**Circumstances Influencing the Prevalence of Dysentery.**—*Latitudinal and Altitudinal factors.*—Dysentery is, in the fullest sense of the word, a ubiquitous disease, being met with in every inhabited region of the globe from the equator to the arctic circle. In a general way, it increases in frequency as we approach the equator. Dysentery is nearly three times more fatal in the south than in the north of France. In the four northern departments of Italy the dysentery death-rate is 0·7, and in the four southern departments it stands as high as 5·1 per 10,000 of the population. The same relation to latitude comes out very clearly in the United States. While in the North Atlantic Coast region the ratio of admission for dysentery in the army for a series of years was 67·0, on the Atlantic Coast of Florida it reached 171·0 per 1000, and the same increase, though less regular, is observed in the interior, from the region of the lakes southwards. But this latitudinal relation is not uniform in temperate climates. Sweden has, until quite recent years, been more liable to dysentery than many countries situated much further to the north; and Ireland might also be quoted as another exception, although here too dysentery has been gradually dying out during the past half century.

In tropical and subtropical countries the prevalence of dysentery is less regulated by latitude than in temperate climates. In the Gaboon, for example, under the equator, dysentery is less frequent than in Senegal, which is situated 13 degrees north; and it is distinctly less prevalent in the southern parts of the south than in the north of India. In warm climates, where the temperature at all seasons of the year is sufficiently high to permit the free growth of the virus in the surroundings of man, the prevalence of the disease is determined less by temperature than by other climatic factors, and by the sanitary and social circumstances of a community.

The influence of altitude on the prevalence of dysentery is perhaps more marked in the tropics than that of latitude. Other things being equal, dysentery decreases as altitude increases. The following figures show the admissions per 1000 for dysentery, according to altitude, in the

European army of India for the years 1895-97. Making allowance for the greater prevalence of amœbic dysentery at lower elevations, the general law comes out clearly enough :—

Below 100 feet	100 to 500	500 to 1500	1500 to 3500	3500 to 5000	5000 to 8000	8000 to 13,000
41·9	32·5	26·3	28·6	18·7	18·9	3·8

*Season and Weather.*—Dysentery, to use Sydenham's expression, belongs to the "true brood" of summer-autumn diseases, and this is true wherever the distinction of seasons is well marked. This dependence on season is most evident in the epidemic dysentery of temperate climates. Hirsch found that of 705 epidemics, 528 occurred in summer, or in summer and autumn; 137 in autumn, or in autumn and winter; 14 in winter; and 25 in spring, or in spring and summer. The determining factor here is indisputably temperature, although other elements, no doubt, come in as modifying influences, the most important of which is supposed to be the diurnal fluctuations of temperature, which set in at the end of summer and are most marked during the autumn months. In most parts of the tropics the seasons are distinguished into dry and rainy, rather than into warm and cold. The alternating periods of drought and rainfall, the effects of which are visible in the changing aspects of the vegetable kingdom, make their influence felt on animal life. Hirsch concludes that rainfall has little influence on the prevalence of dysentery. It would be more correct to say that its influence is variable according to locality and circumstances. The rainfall which in one locality has a beneficial effect by clearing the soil of impurities, leads in another to accumulation of organic matters, forming foci of infection which come into activity as the rains cease. Equally variable are the effects of rainfall on the water-supply. In one locality the rainfall fills the tanks and cisterns with pure water and diminishes the prevalence of dysentery; in another, it produces the opposite effect by washing surface impurities into wells. Fearnside found the number of microbes in the wells of the Cannanore central jail to average 300 to 400 per cubic centimetre during the dry season. When the rain began in June the number rose to 10,000, and increased to nearly 20,000 as the monsoon advanced. In Cannanore, with its excessive rainfall, dysentery is most prevalent during the rainy season; whereas in other parts of the country, where the rainfall is scantier, dysentery prevails during the winter months. In German New Guinea dysentery is most common in the cold rainy months. Wherever, in short, the rainfall leads to soil or water pollution it increases the prevalence of dysentery at the time when this pollution is most marked. Hence the torrential rains which accompany cyclones are so frequently followed by a marked increase in the dysentery death-rate, as was notably the case in Porto Rico after the hurricane of 1899, and in Jamaica after the hurricane of August 1903.

The following rules respecting the seasonal prevalence of dysentery in the tropics hold good generally, but admit of many exceptions. The more equable a climate is, the more uniformly is dysentery

tributed over the different seasons. (2) Where a distinct rainy season exists, dysentery is generally most prevalent when the moist soil is beginning to dry up. (3) A high temperature succeeding a prolonged dry season does not give rise to any notable increase of dysentery until the rains set in. Extreme drought, if long continued, has an inhibitory influence on dysentery. (4) The effects of high diurnal ranges of temperature are most marked at the end of the rainy season, when the body is relaxed by the summer heat.

The following table gives the seasonal distribution of 100 cases of dysentery in the equable climates of Martinique and Cayenne, and in Senegal and Bengal, where the seasons are more sharply defined. The figures, unfortunately, include both the amœbic and bacillary forms of dysentery.

	Martinique	Cayenne	St. Louis (Senegal)	Bengal (Native Army)
January-March	29.40	21.92	18.34	28.1
April-June	25.15	22.25	15.30	13.7
July-September	21.20	28.48	28.39	19.7
October-December	22.16	27.33	37.97	37.35

*Relation to Soil.*—In temperate climates dysentery shews a predilection for moist, marshy districts. It is thus, to use the words of Kelsch and Kiener, that the reports of the Academy continually notice dysentery as occurring in the various departments of Brittany, in the fluvial districts of the Lower Loire and its affluents, in the basin of the Somme, on the plateaux of the Doubs and the Vosges. The southern part of Finistère, Ille et Vilaine, some districts of the Côtes du-Nord, and above all Morbihan, have acquired, in this respect, a sad notoriety. Local epidemics of dysentery often result from the cleaning out of canals and ponds, when the mud is exposed to the action of the sun. An instance of this kind occurred at Leymen (Haut-Rhin) in August 1850, upon the cleaning out of a vast slimy reservoir, situated in the midst of the village. The first cases declared themselves in a few days after the exposure of the mud, and occurred in the houses nearest to the reservoir. The disease spread afterwards to almost every house in the village, dying out only towards the end of October. The mud in this and similar instances was no doubt fecally polluted and contained the virus of dysentery. It is not so certain whether this explanation holds good for those outbreaks (and they are also numerous) which have started from the drying-up margins of a marsh. Sodre states that in the latter part of 1863 dysentery appeared in the city of Rio de Janeiro with an epidemic character, spreading throughout the city and suburbs, and extending to the neighbouring states. This outbreak coincided with the

great excavations made in all the streets of the city in order to lay the net-work of sewage pipes. Here soil-pollution no doubt came into play.

Fæcal pollution of soil is a common cause of dysentery. It has been the experience of armies from the earliest times that dysentery is sure to appear when a camping-ground has been occupied long enough for the soil to become polluted. Pringle relates that when the English army removed from Hanau, where it had been suffering from dysentery, there was such a remarkable decline in the disease "that the change could only be imputed to the leaving behind the infectious privies, the foul straw, and the filth of a long encampment." The gradual increase of dysentery observed in camps occupied for only a part of the year points clearly to progressive soil infection. When the camp at Châlons, for example, was formed in 1857, diarrhœa and dysentery were almost entirely absent, but increased year by year until, in 1864, there were 456 cases of dysentery and 6 deaths; and it is remarkable that, although the active period for the manœuvres opened in May, dysentery only made its appearance in July, and continued until the camp broke up in September, shewing that a certain temperature is required for the growth of the germ. In 1890 dysentery developed almost exclusively in a fraction of the troops assembled at Châlons, and it was found that these occupied exactly the same ground where a regiment attacked by the disease had encamped the year before (Sodré). It is uncertain how long a polluted soil may retain the infection. The history of the camp at Châlons points to the infection clinging to the soil from one year to another.

In the tropics dysentery appears to be more independent of moisture of the soil than in temperate climates, and it may spread in very dry localities. It is certainly remarkable to find that in 1901 dysentery gave rise to 78 admissions per 1000 among the native troops in Aden, with its sun-scorched rocks and burning sands, and only to 41·8 per 1000 amongst those stationed in Colombo with its heavy rainfall. Apart, however, from exceptional instances of this kind, Maclean's statement that "in India dysentery prevails most and is most fatal on moist alluvial soils," is, I believe, true of the tropics generally.

*Relation to Drinking Water.*—Marsh water, not specifically polluted, was believed by Colin to give rise to dysentery, and the use of brackish water has often been similarly accused. According to Parke, the dysentery of Walcheren in 1809 "was in no small degree owing to bad water, which was almost everywhere brackish." The greater prevalence of dysentery in the province of Oran than in the other provinces of Algeria is ascribed to the irritating properties of the water, impregnated with salts of soda and magnesia. The use of surface-water during campaigns in warm climates has frequently been observed to give rise to dysentery. Prof. Simpson, in his report on enteric fever and dysentery in South Africa, states that "the drinking of surface-waters was the most usual cause of dysentery during the war." This is in striking accordance with the observations of Barthélemy in the French expedition to Dahomey. "So long," he says, "as the soldiers drank only river or

oiled water they remained free from the disease, but after hostilities began, and the troops were compelled to drink surface-water, dysentery appeared."

The influence of fæcally polluted water in giving rise to the disease proved beyond all doubt by instances so numerous, conclusive, and well known that we only adduce the following, since it illustrates at the same time the occasional permanence of well-infection. Read states that dysentery broke out in Metz in 1870, and was restricted to two regiments which were found to derive their water-supply from fæcally polluted wells. When these were closed the outbreak immediately ceased. In 1881 (eleven years after) the same barracks were occupied by other troops, and the previously interdicted wells were once more made use of, with the result that dysentery again declared itself, and continued until a pure water-supply was substituted.

The decrease of dysentery which so uniformly follows the supply of purer water in ships and barracks is another proof of the vast importance of water as a vehicle of infection. Dr. Coppinger states that the substitution of distilled for ordinary water in the British navy was followed by a fall in the dysentery death-rate from 12·7 to 1·2 per 1000. The mortality among the Dutch troops in Java for the ten years 1869-78 was 13 per 1000. When water derived from artesian wells was supplied it fell to 1·7 per 1000. In the same way, the decrease of dysentery in the European army in India has kept pace with the increasing attention paid to the purity of the water-supply, as will be seen from the following figures :—

Period.	Dysentery Death-rate.	Period.	Dysentery Death-rate.
1860-69	2·62	1880-89	0·79
1870-79	1·36	1890-99	0·88

*Relation to Food.*—Food is apt to become contaminated by the discharges of dysenteric patients, through the agency of currents of air and insects, especially the common fly.

Dysentery is a constant attendant on long-continued famine, and, arising in this way, it is usually the precursor, in temperate climates, of typhus, relapsing fever, and scurvy. Famine dysentery is not restricted to any season of the year; it rages in winter and spring as well as in summer and autumn, and in temperate climates, especially when attended by typhus, it is in a marked degree communicable. The Irish emigrants in 1847-48 brought the seeds of the malady with them to England, where it spread to some extent among the English population, which was not suffering from scarcity, and they also introduced the infection into America, where it spread widely and continued to prevail for eight years. The effect of the Indian famine of 1897 was to double the cholera mortality, to raise the fever death-rate from 23·13 to 40·98, and to increase four-fold the deaths from dysentery and diarrhoea. The famine dysentery of India does not exhibit the infectious character observed in the famine dysentery of temperate climates. Scarcity, not amounting to famine,



especially when combined with other hardships, predisposes to dysentery. Col. Robertson relates that during the South African war the Eighth Division had to make long and rapid marches on half rations. "The result was severe dysentery, even when not in a standing camp," that is, when soil-infection did not come into play.

The use of improper food is an incident of all famines, and it is impossible to say to what extent inanition and the use of unsuitable food, respectively, are responsible for the outbreak of famine dysentery. Perhaps it was not without reason that the ancients more frequently ascribe the dysentery of famine times to the use of "corrupt food" than to actual want. Herodotus attributes the dysentery which destroyed the retreating forces of Xerxes to their eating herbage and the bark and leaves of trees, not to starvation. Instances might be given in which musty, mildewed cereals, tainted animal food, coarse food not actually unwholesome, and the use of unripe or decomposing fruits have appeared to give rise to dysentery in countries and seasons where the disease is endemic. Major Buchanan has often found outbreaks of dysentery in Indian jails to coincide with the issue of badly cleaned or badly cooked cereals. One of the old English synonyms of dysentery, as Dr. Creighton points out, was "surfeit," indicating that our ancestors connected dysentery with excesses in certain articles of food, this, indeed, may have been the case at a time when the germ of dysentery was widely diffused throughout the country. It is certain that excesses of this kind do not give rise to dysentery in England at the present day, but they are not equally harmless in tropical countries where dysentery is prevalent.

*Relation to Fatigue and Exposure to Alternations of Heat and Cold.* Fatigue, hardships, and exposure, if long-continued, are sufficient of themselves to give rise to pseudo-dysentery, and they powerfully dispose to true dysentery. Hence dysentery is an inseparable attendant on war in all climates and at all seasons of the year. Dysentery was one of the most fatal diseases both in the Russian and Allied armies in the Crimea (1856-57). Along with diarrhoea, dysentery constituted a third of the total admissions of the Federal army during the War of Secession, i.e. two out of six millions. In the Franco-German war (1870-71) there were 38,652 admissions and 2380 deaths from dysentery in the German army. In South Africa, during the first two years, the dysentery admissions numbered 24,274 and the deaths 975. Even in the non-malarial climate of New Zealand the troops, when subjected to hardships and compelled to lie out in the wet at night, suffered from dysentery. Sir John Pringle's account of the circumstances in which dysentery broke out among the British troops in June of 1743 is very instructive. The army, we are told, marched all night and fought next morning at Dettingen. Then the weather, which had previously been very warm, changed and became cold and rainy. After the battle the men lay on the ground, without tents, exposed to a heavy rain. Next day they marched to Hanau, where they encamped on wet ground, without straw. "In the space of eight days after the battle about 500 were seized with



ntery, and in a few weeks near half the troops were either ill or had  
 vered from that distemper. It was common, though not nearly so  
 ent, among the officers, of whom those were first seized who hap-  
 l to lie wet at Dettingen; the rest suffered by contagion." Two  
 nies in charge of the King's baggage, encamped at a short distance  
 the main army, eating the same victuals and drinking the same  
 escaped, as they had not been exposed to the same fatigues, and  
 rain and wet. But after six weeks, when these two companies  
 the main body, they were at last infected. The sick were  
 the village of Feckenheim, about a league from the camp, and  
 he disease was communicated to the rest of the patients, to the  
 and apothecaries, and to most of the inhabitants of the village.  
 same way the dysentery-stricken soldiers of the German army, on  
 return home in 1871-72, established foci of infection in many  
 es, which have not yet become entirely extinct.

*Relation to Malaria and other Diseases.*—It is needless to adduce  
 e that malaria and dysentery are perfectly distinct infections,  
 y often prevail in the same localities, and malaria disposes to, and  
 nes aggravates, dysentery. Major Buchanan (13) states that the  
 ortality of dysentery in the jails of India for the years 1896-97  
 3 per cent, whereas in the extremely malarious year 1894, in certain  
 for which he obtained the figures, it was as high as 9 per cent.  
 o diseases often coexist. Dysentery is a frequent termination of  
 maladies—pneumonia, phthisis, kala azar, cerebro-spinal meningitis,  
 and surgical cases. Intestinal worms, by irritating the bowel,  
 ieved to favour the development of dysentery. Their presence,  
 ng to Nothnagel, leads to a marked increase of bacteria in the  
 ia neighbourhood of the parasites. These bacteria are not always  
 thogenetic, and they may readily invade other parts of the in-

*Modes of Spread—Contagion and Infection.*—Direct contagion in  
 ery is practically restricted to cases in which an enema syringe,  
 or a dysenteric patient, is employed for giving an injection to a  
 with some other disease without being previously cleaned, and  
 s due to the introduction of contaminated fingers into the mouth.  
 read of dysentery in hospitals is usually less direct. The bed-  
 utensils, floors or walls of the ward become soiled by dysenteric  
 ons, and the virus is conveyed to other patients by food, water, or  
 f we are justified in speaking of the transmission of dysentery by  
 ma syringe as contagion, we are clearly none the less so when the  
 nds its way by a more indirect route from the dysenteric to the  
 bowel. Indirect contagion is a common mode of spread in the  
 ic dysentery of temperate climates, especially in the homes of the  
 A large family is frequently crowded into one or two apartments,  
 the arrangements for the safe disposal of the stools and for securing  
 tection of food from pollution are necessarily defective. In these  
 stances it is the rule for several members of a household to be

seized in succession. Blanche records an instance in which dysenteric stools were thrown upon the street, with the result that a number of the inhabitants were simultaneously seized with the disease—multiple cases occurring in most families. Here we have still to do with indirect contagion, the immediate source of the virus being the dysenteric stool. Indirect contagion is also the common mode of spread in institutional dysentery. The disease was introduced into Cornwall in 1899, and gave rise to a house epidemic. Ogata has published the particulars of numerous cases in which he clearly traced the spread of the disease in Japan to intercourse with the sick, especially by visiting them in their homes. The introduction of epidemic dysentery into a town or country has in not a few instances been traced to the arrival of a dysenteric patient. A labour vessel from Queensland landed a native woman with her half-caste child, suffering from dysentery, at Futuna, one of the New Hebrides. The disease soon spread all over the island, and cut off one-fourth of the population (22). An epidemic in Norway in 1859 was definitely traced to the return of a sailor who had been treated for dysentery in Liverpool. The disease spread from the home of the sailor and attacked in all 3992 persons, of whom 621 died. Ship-dysentery, of which there are numerous instances, is probably spread in this way.

The case is different when an independent focus of infection is set up in house, cesspool, or soil, capable of propagating the disease for an indefinite time. The origin of the virus has probably been the dejections of dysenteric patients, but the pathogenetic agent, in becoming adapted to saprophytic conditions, gives rise to an autonomous source of infection. To the account of infection may be placed those outbreaks in which a faecally polluted soil has retained for months or years the power of generating the disease; those in which mud from faecally polluted ponds, canals, or the desiccating margins of lakes has been the starting-point of an epidemic. To infection, also, we refer the instances in which a faecally contaminated well has retained its infective properties long after the disease has been absent from the locality. The instance of Metz, already noticed, is an example of this kind.

These two modes of spread—contagion and infection—are simultaneously in operation in many outbreaks, but in epidemic dysentery the preponderating factor appears to be contagion. In the endemic dysentery of tropical countries, on the other hand, contagion is so little in evidence that many of the most experienced physicians have doubted its existence. One can hardly suppose this property to be altogether absent from the endemic disease, but I do not remember any instance in which dysentery was clearly communicated by contagion in hospital.

Pfuhl found the bacillus in the dysenteric stools of soldiers from China a year after their return to Germany. The risk, therefore, of patients suffering from chronic dysentery spreading the infection should not be overlooked. The sources of the virus are thus practically the dysenteric stools and the infectious foci set up by them. We do not

whether any of the lower animals harbour Shiga's bacillus, but it has often been epizootic and epidemic at the same time. The food and agents for its diffusion are the dysenteric patient himself, food, air, and insects. The ports of entrance are the mouth and rectum, perhaps, the anus; in one instance a culture of Shiga's bacillus in contact with the conjunctiva, and was followed in twenty-four hours by dysentery (Dodge).

**Personal Factors—Age.**—All ages, from the nursing child to extreme old age, pay their tribute to dysentery. In some of the European countries nearly half the attacks and rather more than half the deaths have been among children. The dysentery death-rate of Indian children in India, for 1901, was 2·56, while that of the soldiers was 0·97. The Bombay statistics shew that native children under five years of age furnish a high ratio of deaths; from 5 to 15 years the ratio decreases, to rise again in adult life. Strack and Zimmermann state that they had seen children, born of mothers suffering from dysentery, come into the world with the disease. Markwald states that Shiga's bacillus was found in the heart's blood of a foetus of seven months, the mother was suffering from dysentery, and that the early lesions of dysentery were found in its intestine.

—In Europe both sexes appear equally liable to the disease, but in some epidemics women have suffered most. The ratio of deaths among the European women belonging to the army in India was more than half that of the men. This disparity is not dependent on habits of life and exposure to the predisposing causes. Native women of the large Indian towns, for the same reasons, shew a rather lower dysentery mortality than the men. How it stands in rural districts, where women take their share in outdoor labour, is uncertain.

—All races are equally liable to dysentery. The differences observed in the death-rates of various nationalities living in the same country depend, not on race, but on habits and social conditions. Among all races the disease is often highly destructive. Dr. Seligmann states that epidemic dysentery to be exceedingly common and very fatal among the native tribes in British New Guinea. In some villages it had killed off 15 per cent of the inhabitants, and he came upon a group of natives who had deserted on account of dysentery. Witness, too, the extermination of some of the Indian tribes in British New Guinea by the allied disease known as epidemic gangrenous proctitis.

**Occupation.**—Dysentery is more a disease of country hamlets and villages than of cities. Agricultural labourers are more liable than those engaged in indoor occupations. Of town populations, according to Zancanolli, cooks, and mechanics exposed to great heat are specially predisposed. Soldiers, sailors, and explorers in tropical countries pay a heavy tribute to dysentery.

**Social Condition.**—Dysentery is notably a poor man's disease. The rich suffer less than the poor, the officer than the private soldier.

The scantily clad, the poorly fed, the badly housed, the overworked, always furnish the largest quota of victims to the disease.

*Effect of Length of Residence in the Tropics.*—European soldiers recently arrived in India shew a somewhat greater liability to dysentery than those whose residence has been longer, but after the seventh year the deaths from dysentery increase according to length of service, in proportion to the total deaths from all causes, as will be seen from the following table by Bryden, shewing the ratio of deaths from dysentery to 100 deaths from all causes according to length of service :—

First year.	Second year.	First 5 years.	Fifth to seventh year.	Above 7 years.	Above 10 years.
9·6	10·4	9·0	10·1	13·3	13·7

It is evident that there is no acclimatisation for dysentery.

**Mortality.**—The case-mortality among the British troops in India for the ten years 1891-1900 was a little under 3 per cent, and that of the native army for the same period somewhat lower. In the jail hospitals of Bengal, according to Major Buchanan, it was 3·8 per cent for the years 1896-97. These figures do not convey the impression that the dysentery of the barracks and jails of India is a disease of any great gravity, and they contrast in a very striking way with the high case-mortality of epidemic dysentery in Europe and Japan, and with that of the endemic disease of tropical countries generally, as derived from the returns of civil hospitals. Strong and Musgrave, in the Philippines, distinguish from specific bacterial and amœbic dysentery a mild catarrhal form which is rarely fatal. This, I take it, is pseudo-dysentery. It seems probable that many cases of this kind are included in the returns of military and jail hospitals. The case-mortality in six epidemics of dysentery in France and Germany of which I have the particulars ranged from 9·0 to 14·9 per cent. An instance is recorded by Maggiora of an epidemic at Grazzano in Italy, in 1888, in which out of 2001 patients only three deaths occurred, but this is altogether exceptional. The case-mortality in Japan, according to Shiga, varies from 16·5 to 30·9 per cent. In the Ceylon hospitals, for 1903, it stood at 28·7; in British Guiana, in 1902 and 1903, at 22·8 and 26·6 per cent respectively. In Singapore, where we have been taught to believe that dysentery is of a mild type, the hospital mortality in 1902 was no less than 25·4, and in the neighbouring State of Selangor it reached 34·0 per cent. In Trinidad it stood at 30·7, in German New Guinea at 33·0, and at Hong-Kong, in 1902, it reached 37·3 per cent (17). No doubt the fact that in military and jail hospitals the patient comes under treatment at once, whereas the civilian is seriously ill before he seeks admission into hospital, goes a very considerable way in explaining the lower death-rates in military and jail hospitals. But the discrepancy is too great to be accounted for in this way. Are we not justified in suspecting that a considerable proportion of the cases returned as dysentery in the military and jail hospitals are nothing more than a simple catarrh of the large intestine—

such as those referred to by Strong and Musgrave, which would have recovered by rest and dieting without medicine? If this view be correct, and different diseases are included under the term dysentery, it is obvious that caution must be exercised in judging of the value of different methods of treatment from such statistics. A. D.

**Bacteriology—Historical.**—The occurrence of bacteria in the stools and tissues in dysentery was demonstrated by Klebs, Prior, and Ziegler, who worked, however, either with faulty bacteriological methods or merely with sections of tissues. Ziegler, from examination of the microscopic tissue-changes, came to the conclusion that the relationship of the bacteria to the lesions shewed that the bacteria present had had a pathogenetic action. Hlava isolated nineteen kinds of bacilli from the discharges of cases of epidemic dysentery, but none of these reproduced the lesions of dysentery in animals. The later investigations were more successful, since they dealt with pure cultures of particular forms or species of micro-organisms. The most important are those of Chantemesse and Widal, Maggiori, Laveran, Arnaud, Celli and Fiocca, Galli-Valerio, Valagussa, Grigoriew, Escherich, and Deycke, all of whom obtained from the stools of patients or intestinal contents at post-mortems certain colon bacilli which were especially distinguished by enhanced virulence. At the present time the colon bacillus is not believed to be one of the direct causes of dysentery, and the property of increased pathogenetic action for lower animals is now known to be acquired by this bacillus in many pathological states existing in the intestine in man. The bacillus isolated by Ogata in Japan could not be obtained by other bacteriologists, and the notion that pathogenetic cocci cause dysentery, as brought forward in the work of De Silvestri, Bertrand and Baucher, and Ascher, has now been discarded. That the *Bacillus pyocyaneus* can, under certain conditions at least, cause dysentery would seem to be proved by the results of Calmette's work on the endemic entero-colitis of Cochin China, and of Lartigau and Adami's on small localised epidemics of dysentery in the northern United States and Canada. Of these investigations the most important are those of Celli and Fiocca, and Del Pino and Alessandri, all of whom studied varieties of *Bacillus coli*, which were not only pathogenetic for certain small animals, but produced dysentery in cats, and yielded active toxins also capable of setting up these lesions; and those of Escherich upon contagious colitis in children, which he regarded as caused by a variety of the colon bacillus.

These bacteria, with the possible exception of the bacilli of Chantemesse and Widal and of Ogata, so far as they could be studied in cultures, shewed no specific properties. They all represent well-known bacterial species, constantly present normally in the situation from which they were obtained in disease, their only unusual properties being increased virulence when tested upon animals, and a capacity to set up enteritis when injected into the intestine in dogs and cats.

An investigation of Japanese epidemic dysentery in 1898 by Shiga

yielded different and more convincing results. He recognised at the outset that the *Bacillus dysenteriae* must fulfil four essential etiological conditions: (1) it must occur constantly; (2) it must be a species not normally present in the diseased organ; (3) it must be pathogenetic and produce in experimental animals lesions similar to those from which it was obtained; (4) it should, by reason of its pathogenetic action in man, shew the agglutination reaction with the blood of patients suffering from dysentery. From the series of cases studied by Shiga a bacillus fulfilling these requirements was isolated.

**Bacillus dysenteriae (Shiga).**—The dysentery bacillus, so-called, does not represent a single hard and fast species, but a group of closely related bacilli. At present two distinct and several subsidiary types are recognised. The two main types are the Shiga and the Flexner or Manila. They came respectively from the dysenteric diseases prevailing in Japan and the Philippine Islands. It is highly probable that both these types appear in each of these countries, as was proved to be the case in Germany by Kruse, and in the United States by myself and my pupils, Vedder and Duval. That, moreover, the two types may be associated in the same individual has been shewn by Gay and Duval working in my laboratory in Philadelphia. The criterion of the *Bacillus dysenteriae* is its pathogenetic action in man under the conditions formulated by Shiga. On the basis of this test no etiological distinction can be drawn between the main types and certain, at least, of the subsidiary types of the bacillus.

The morphological characters are similar in all the types. The bacillus is a short rod about the length of, but somewhat plumper than, the typhoid bacillus, with rounded ends. From this prevailing form there are variations. Sometimes, especially in very young cultures, the bacilli are very short; again they shew irregularities of staining, and not infrequently they are united in pairs or short chains, or lie in irregular clumps. The bacillus stains readily with the usual dyes, and is decolorised by Gram's method. It is asporogenous. Considerable difference of opinion has prevailed as regards its motility. Shiga and Flexner described slight locomotion in young cultures, but the general opinion of later bacteriologists is opposed to this view. Duval and Vedder describe peritrichal flagella, and invented a method for demonstrating motility in the bacillus recently isolated from artificially infected guinea-pigs. Cultures obtained from cases of human dysentery are usually non-motile, unless the examination be made of young growths (16 to 18 hours old) in the first generations. Saprophytic cultivation seems quickly to deprive the bacilli of motility, although the flagella persist.

The cultural characters of all the types are essentially the same, but there are certain distinctive differences which are of use in separating them. The dysentery bacillus grows readily upon the usual cultural media, and most actively at the temperature of 37° C.; at room-temperature its growth is slower, and it ceases entirely to multiply at 6° C. The usual media employed in its cultivation are agar-agar,



tin, bouillon, and milk. The growth on potato and on sugar-agar broth is, however, useful for purposes of identification and differentiation. Upon agar-agar the organism grows as an opaque white line along the stab, and spreads slightly at the surface; after several days growth may extend over the entire exposed surface of the agar-agar. A single line of growth on the agar-agar slant tends to remain restricted to a narrow middle zone of the medium, where it forms a slightly elevated, brownish, opaque layer of 3 or 4 millimetres in width. The growth becomes thinner towards the peripheries, and the edges are scalloped. Illuminated with transmitted light an appearance suggesting the branches of a tree is to be made out. The growth upon agar-agar, excepting for slightly greater abundance, closely resembles that of the typhoid bacillus, but as compared with that of the colon bacillus it is less in amount and has a more delicate appearance. The colonies on agar-agar begin as round or elliptical points, which may attain the size of 1 to 1½ millimetres in twenty-four hours. Those which reach the surface tend to spread until, after several days' growth, they may reach a centimetre or more in size. They are translucent, and in consistence and opacity intermediate between typhoid and colon bacilli colonies. Gelatin is not liquefied. The colonies on gelatin of 10 per cent, or even greater concentration, begin as small round or oval, faintly yellowish-brown points, and slowly increase in size. On the surface they spread, become transparent, and assume the grape-like appearance of typhoid bacillus colonies. The larger agar-agar and gelatin colonies shew an eccentrically placed nucleus. Stab-cultures grow along the line and spread on the surface. Bouillon is rendered turbid, and sedimentation occurs. A membrane is not, as a rule, formed. Starch production is absent in the original Shiga cultures, but it is produced by other varieties of the bacillus. Milk is slightly acidified, and is rendered amphoteric or faintly alkaline. These changes can best be observed in litmus milk. No coagulation takes place. On potato the growth is slight and membranous, and is either visible or invisible according to the reaction of the potatoes employed. Should the potatoes be alkaline no growth can be seen; but if alkaline an elevated brownish layer is formed.

*Fermentation.*—No gas is formed in any of the sugars. The original Shiga bacillus ferments, of the many sugars tested, dextrose and other mono-saccharides, producing acids and causing distinct reddening of a glucose-litmus culture medium. If instead of litmus-glucose-agar or bouillon the serum-water medium of Hiss, containing glucose, be employed, the Shiga bacillus will produce reddening and coagulation of fluid.

All other types of the dysentery bacillus have wide fermentative properties. The Flexner or Manila type, which seems to possess the least capacity, ferments dextrose, mannite, saccharose, maltose, and dextrin, but not lactose. The subsidiary bacillus of Hiss and Russell, which belongs to this group, fails to ferment dextrin. The number of variants among this group of bacilli is considerable, and it is probably

incorrect to continue the subdivision into types indefinitely. The manner in which this whole class of organisms agrees and differs is of interest and cannot fail to arouse the suspicion that our knowledge of its physiological properties is at present in a very unstable condition.

*Agglutination.*—Agglutination reaction has been of great importance in the original separation of the bacillus of dysentery from admixture with the other intestinal bacteria, and it has been employed in the subsequent study of the types of the bacilli. Kruse was the first to point out a marked variation in the degree of agglutination between different strains of dysentery bacilli. The two strains which he studied came respectively from an epidemic of dysentery and several cases of the disease which arose in an institution for the insane. The blood of patients suffering from epidemic dysentery agglutinated the first strain in higher dilutions than the second, and the blood of animals immunised to the bacillus isolated from the epidemic cases behaved in a similar manner. On the basis of the observed difference Kruse designated the former as "true" and the latter as the "pseudo"-dysentery bacillus. These appellations are unfortunately chosen, and more searching study has already dissipated the notion of a distinct etiology for epidemic and institutional dysentery. The anatomical lesions and clinical symptoms are the essential facts upon which the diagnosis of dysentery is based, and these are in entire agreement in the two classes of cases. There are no "true" and no "false" dysentery bacilli, and the term "dysentery bacillus," like the term "cholera bacillus," must now be taken to include several types which are closely related in morphological and cultural properties, but which shew variation in fermentative and agglutinative qualities. They possess, however, the most essential feature in common of being able to set up in man the lesions of pseudo-membranous and ulcerative dysentery.

The absorption of agglutinins from an active dysenteric serum by any of the bacillary types will remove the major or minor part of the agglutinins present, depending upon the type of bacillus used in immunisation. The major agglutinins are the more specific ones; the minor are produced indifferently by any of the types, and similar ones—the so-called "common" agglutinins—may even exist normally in the blood of certain animals, *e.g.* the horse. Hence the absorption method of Castellani has been employed to assist in the establishment of "types" of dysentery bacilli.

Shiga first applied the Neisser-Wechsberg method of bacteriolysis to the study of dysentery bacilli, but his observations had no reference to the differentiation of the types. Gay, later, found that perfect bacteriolysis depended upon the employment of bacilli and immune serum of corresponding types. Neither immune serums nor types of bacilli were interchangeable in producing bacteriolysis, from which the conclusion that bacteriolytic variations serve to distinguish the types of bacilli could be drawn. Dopter has employed the method of Bordet and Gengou of absorbing the hæmolytic alexin in immune dysenteric serum for determining the

onship, and has reached the conclusion that all bacilli of dysentery members of one large group, in which they behave as more or less distinct species.

It has been observed that cultures of typhoid bacilli and other organisms isolated from the blood and internal organs shew a condition of agglutinability. After successive cultivations on artificial media a tendency for agglutination may appear. Marshall and Knox found by cultivating the dysentery bacillus in bouillon containing antidysenteric serum that it became, for the time, inagglutinable. Subsequent growth on agar restored the agglutinability.

**Immunisation.**—Small and large animals may be immunised actively or passively to the dysentery bacillus. For active immunisation guinea-pigs are well adapted; and for passive immunisation goats and horses are employed with advantage. From the latter animals large quantities of serum for therapeutic uses have been obtained. As the finer differential methods are separating the different types of bacilli from each other, the question has arisen whether the behaviour of the types is equally distinct with respect to the protective effects produced in the animal body by the various serums. Upon the answer given to this question may depend the practicability of using antidysenteric serum therapeutically in man.

Flexner made an exact study in guinea-pigs of cross-immunisation by serum yielded by the Shiga and Flexner strains of dysenteric bacilli, and found that the protective power of the serum is a factor which does not proceed hand in hand with bacteriolysis and agglutination, and that the latter phenomena are not measures of the possible therapeutic usefulness of the serum. But since each immune serum is most effective against its own type of bacillus, a polyvalent serum is more likely than a monovalent one to be useful in therapeutics.

**Resistance of Dysentery Bacilli.**—Dysentery bacilli can be cultivated readily, but they do not survive indefinitely upon old cultures. The period of survival is not a fixed one, but depends, in part, on the strain of bacillus, the composition of the medium, and the mode of preservation. Under similar conditions certain strains will survive many weeks, while others will be found to have ceased to grow on transplantation after one or four weeks. On media free from fermentable sugars, or containing small percentages of sugar, especially if drying be prevented, all strains will survive four weeks or longer; but in the presence of the acids produced from sugars the period of viability is greatly reduced, and some strains will succumb after one or two weeks.

In competition with many saprophytic organisms the dysentery bacilli quickly disappear, as, for example, the saprophytes of the faeces and the common acid-producing bacteria of milk. They cannot be cultivated, as a rule, after two days' sojourn in faeces or eight days in milk (Kruse), even if the mixtures have been kept on ice. Schmidt failed to isolate the dysentery bacillus from mixtures of earth, water, or faeces exposed to winter cold, while Pfuhl, who mixed faeces containing dysentery bacilli with earth and kept them at a temperature of 1.5° C.

to 15° C., was still able to cultivate the dysentery bacillus after 101 days. When cultures are mixed with fæces in the air-dry condition they survive twelve days, and in linen soiled with fæces seventeen days. In water the period of survival varied from five to nine days, and in butter and cheese it was about nine days. The bacilli are killed in half an hour by 1 per cent, and immediately by 5 per cent carbolic acid and 1:1000 solution of corrosive sublimate.

*Variation in Virulence.*—In artificial cultures the dysentery bacillus is apt to diminish in virulence for laboratory animals. This is true, apparently, for all types of the bacillus. The minimal fatal dose of freshly isolated cultures of the Shiga strain is often as low as  $\frac{1}{16}$  loops, and of the Flexner strain of  $\frac{1}{4}$  loops, as measured by guinea-pigs of 250 grammes in weight. After some weeks of saprophytic cultivation the fatal dose may have increased to one or two loops, and after many months to one or more slant agar-agar cultures. The virulence for guinea-pigs can frequently be restored more or less completely by passage from guinea-pig to guinea-pig in rapid succession. The transfer should not be made directly from animal to animal, but intermediate cultivation is always necessary. The readiness with which the dysentery bacillus loses and reacquires virulence is not without importance in connexion with a grasp of the problems of the epidemiology of bacillary dysentery.

*Method of Isolation of Bacillus dysenteriae.*—The dysentery bacillus is isolated with greater or less difficulty from dejecta, and directly from the mucous membrane; the determining factors being the relative number of the bacilli originally present, and also the freshness of the preparation and the method employed. If stools are employed they should be examined immediately after they have been passed; scrapings of the mucosa of the intestine will yield the bacillus twenty-four hours or longer after death. But the rule in all cases is to make the bacteriological examination at the earliest practicable moment.

Mucus or mucus tinged with blood is to be selected for plating in agar-agar. The material is suspended in sterile saline solution or bouillon, well shaken, and set aside for a few minutes to permit the larger flocculi to subside. From the cloudy suspension 10 to 12 agar-agar tubes are inoculated with different quantities, and as many Petri plates made. The seeding of the plates is a matter of importance, and the total number of colonies developing upon a plate should be preferably between 50 and 100. The plates are incubated for fourteen to eighteen hours at 37° C. At the end of this period every small pearl-grey colony is transferred to a glucose-agar stab tube or to a tube of Hiss's semi-solid medium. All the colonies are now marked on the glass with a wax pencil, and plates kept inverted at the room-temperature for several days. When colonies develop they are transferred in this manner. The inoculated tubes are ready for examination after six hours in the thermostat in the case of Hiss's medium, and twelve hours in that of glucose. In the case of the latter all tubes shewing gas-formation, and in the case of the former all shewing diffuse cloudiness, caused by active

Bacilli, or gas-bubbles, are discarded. Sometimes the gas is not liberated in this medium until it is gently stirred with a platinum needle. The selected tubes are now examined microscopically. All those showing bacilli are tested, if possible, with antidysenteric serum or the patient's blood, for agglutination. All bacilli shewing the agglutination reaction are sub-cultured into litmus-milk and the different sugar culture media. Since certain strains of dysentery bacilli agglutinate poorly or not at all in the early isolations from human beings, this test is not absolute. Cultivation in the various differential media may be resorted to without testing for agglutination, or when it fails to appear. The identification of the bacillus depends upon morphological and cultural properties, upon the fermentative and agglutinative reactions, and, to a less extent, upon pathogenetic action in animals.

*Bacillus Dysentery in Man.*—The Shiga bacillus has been obtained in all parts of the world in which epidemic dysentery has been studied bacteriologically. It may, therefore, be accepted as the etiological organism of this disease; and it equally is the cause of a part—the non-amoebic part—of the endemic disease of the tropics and sub-tropics, and the sporadic disease of temperate climates. The bacillus occurs throughout the intestine, although it is present more frequently or in larger numbers in the lower bowel in which the lesions are situated. It is usually associated with *B. coli*, and often with other intestinal bacteria, so that its isolation is often a matter of difficulty. Cases have, however, been described in which the bacillus has appeared in pure or nearly pure cultures on the plates. In the intestine the dysentery bacillus occurs on the surface and in the contents of the gut, but, in the deeper parts, within the crypts of Lieberkühn and in the substance of the mucosa, it penetrates further than the saprophytes. Hence it is frequently more certainly and readily obtained at autopsy from scrapings of the intestinal mucosa freed from fecal covering, even though visible mucus are absent in the parts, than from the dejections during life. Duval has obtained the bacillus from an excised portion of the intestine which had been on ice about forty-eight hours after death. The dysentery bacillus survives in the tissue longer than in dejecta, since in the former situation it is less exposed to the competitive action of the intestinal saprophytes. In dysentery the Shiga bacillus can frequently be isolated from the mesenteric glands and more rarely from the liver. The other viscera and the blood would seem not to harbour the bacillus, which, it must be assumed, escapes from time to time into the circulation. The number of bacilli in the lymph-glands and liver is, judging by the difficulties of cultivation, not large. In order to obtain cultures considerable portions of comminuted tissue should be transplanted to agar-agar and poured into plates. The dysentery bacillus, even in these situations, is accompanied at times by the colon bacillus, which in fluid cultures is likely to overgrow the former. These secondary loci of settlement of the dysentery bacillus do not appear to be centres of active multiplication. The bacilli are difficult to demonstrate in



sections of mesenteric glands and liver, but this may be ascribed either to small numbers or to failure due to the want of a selective staining method. Whether these localisations play an important part in the production of the constitutional symptoms of dysentery is not known. The dysentery bacillus produces an active poison, which causes not only the constitutional symptoms but also the local intestinal lesions of the disease. Hence every focus of development of the bacilli within the body adds materially to the toxic effect produced by the bacilli developing in the intestinal wall and contents.

The questions of priority of discovery and confirmation of the bacillus of dysentery have aroused much discussion. Those who have participated chiefly in the contention are Chantemesse and Widal, Celli, Shiga, and Kruse. According to our present knowledge neither Chantemesse and Widal (1888) nor Celli (1896) could have been dealing with the Shiga dysentery bacillus. The former authors state that their bacillus, when administered by the mouth or injected into the rectum or into the intestine after laparotomy, or even introduced by direct intraperitoneal inoculation, sets up in guinea-pigs intestinal lesions resembling the dysenteric lesions in man. It is now definitely established that none of the types of the dysentery bacillus is capable of producing diphtheritic or ulcerative intestinal lesions in the guinea-pig by any of these methods of administration. This discrepancy would alone suffice to shew that the bacillus of Chantemesse and Widal was not identical with Shiga's bacillus; but it is also impossible to identify them by means of the cultural properties described. As for the dysentery organisms originally described by Celli and later by him and Fiocca and Valenti, it is clear that they belong to the colon bacillus group, since they not only ferment sugars with the formation of gas, but bring about coagulation of milk. Later Celli isolated the true dysentery bacillus; but this was after Shiga, Flexner, and Kruse had described the organism. The contention on priority between Kruse and Shiga is about Shiga's careful studies were published in 1898, and Kruse's first communication appeared in 1900; and between these two publications Flexner and Barker's report (February 1900) on a medical expedition to the Philippine Islands appeared. In this report the isolation of the Shiga bacillus from cases of acute dysentery occurring in Manila was announced. The present basis of disagreement between Kruse and Shiga refers chiefly to the question of motility of the bacillus, regarding which no definite conclusion has been reached (see p. 490).

In 1898 Shiga published the results of his study of epidemic dysentery of Japan. In 1897 there were 89,400 cases with 22,300 deaths. In 36 cases investigated bacteriologically the dejecta or intestinal mucosa yielded the bacillus now bearing his name. It differed from the other organisms isolated from the intestine in agglutinating with the patient's blood in moderate dilution—1:20-50 to 1:130. In the more severe cases the agglutination was usually in 1:50 dilutions or over; in the mild ones it was weaker or absent. Lethal cases agglutinated weakly. It was difficult to obtain the bacilli early in the disease, but at a later period the mucous and bloody stools might yield almost pure cultures. They were plentiful in the intestinal mucosa and in fresh catarrhal or pseudo-membranous lesions, and the deeper layers of the ulcers gave almost pure cultures. Shiga found the bacilli in the mesenteric glands but not in the liver or spleen. In 1901 he stated that an immune serum produced by



ulation of the bacillus into horses possessed protective and therapeutic effects in human beings. He inoculated himself with a culture of the dead bacillus which, while it developed agglutinins in his blood, set up a very painful local reaction.

In 1900 Flexner's full paper appeared. He described two types of bacilli constantly present in the dejections of patients suffering from acute non-amoebic dysentery. The first was identified with the Shiga bacillus, the second *Bacillus coli communis*. Of the first he states that suitable cultures, when used for the agglutination reaction with the blood-serum of persons suffering from dysentery—the host or another individual—give, in many cases, a positive result. The bacillus was abundant in the acute cases in which it may be the dominating organism; it became progressively more difficult to find as the case passed into recovery or chronicity. It was cultivated from the dejecta during life and the mucous membrane and mesenteric glands in fatal cases.

The second bacillus varied in agglutination reaction as the blood of the host or another individual was employed. With that of the host there was frequently a reaction in low dilutions; with that of another person it was rarely obtained. Strong and Musgrave (1900) continued the bacteriological study of dysentery begun by Flexner and Barker in Manila, and secured from other cases a bacillus proved by them to be *B. dysenteriae* (Shiga). They propose for the disease of bacillary origin, in order to distinguish it from the amoebic disease, the name acute specific dysentery. Strong and Musgrave give an admirable clinical and pathological description of bacillary dysentery, but their bacteriological findings were merely confirmatory. They studied the serum reactions of 246 cases of diarrhoea and dysentery, without regard to type of disease, against the dysentery bacilli isolated by them. Of these 71 cases gave prompt agglutination in 1:10 dilution; and they either had suffered recently or were suffering at the time from acute dysentery. The stools of 21 of these cases yielded upon examination the dysentery bacillus. In three of the cases with positive serum reactions amoebae, and in two others *Trichomonas intestinalis*, were found in the stools. The first are regarded as examples of mixed infection of *B. dysenteriae* and *Amoeba coli* (*dysenteriae*); but as the dysentery bacillus was not actually obtained from the dejecta, they remain doubtful.

Flexner (1901) extended his investigations of dysentery to the sporadic and institutional disease occurring in America. The studies were made by Vedder and Duval, who obtained the dysenteric bacillus from sporadic cases of the disease occurring in Philadelphia, Pa., and two institutional epidemics at New Haven, Conn., and Lancaster, Pa. They identified the bacilli obtained by them with Shiga's Japanese and Flexner's Philippine cultures.

Kruse (74) (1900) published his first communication on the etiology of dysentery, based on the study of an epidemic of the disease and several sporadic institutional cases. The organism obtained from the former has now been identified with the Shiga Japanese bacillus; and from the latter with Flexner's Manila bacillus. Kruse denied all motility in the dysentery bacillus isolated from him. Serum tests were made. The serum of patients after the seventh day agglutinated regularly in a dilution of 1:50; and many reacted as high as 100-250. One serum reacted in 1:1000 dilution. Twenty-five normal persons were negative or positive only at 1:10-20 and occasionally at 1:50. In 1901 Kruse's second paper appeared. He discarded his result of 1:50 agglutination in normal persons, preferring to believe them the subject of a

previous infection. He pointed out that Flexner's Manila culture reacted differently to human dysenteric and animal immune serum from his bacillus obtained from the epidemic cases, while it agreed with the bacillus obtained from institutional cases. These latter cases he called "pseudo-dysentery of insane asylums," and proposed for the bacillus obtained from them the name of "pseudo-dysentery" bacillus. He studied the stools of twelve and the intestine from two insane patients. In these fourteen cases he failed to isolate an organism corresponding in all characters to the true dysentery bacillus; but from three cases (one patient and two autopsies) he obtained bacilli culturally like the "true" dysentery bacillus, but differing in serum reactions. These bacilli agglutinated 1:100 in serum from the insane patients, and often 1:50 in normal serum. To the former serum the Shiga or true bacilli failed to respond. The former organisms differed in certain reactions not only from the bacillus of epidemic dysentery, but even among themselves. Kruse's studies form the starting-point for the differentiation of the dysentery bacillus into types, which has now been done on the basis of agglutination and the fermentation of sugars. The chief researches, next to those of Kruse, upon which the differentiation has been based, are those of Martini and Lentz, who separated the mannite-fermenting pseudo-dysentery bacilli so-called from the Shiga dysentery bacillus. Martini and Lentz expressed the opinion, based upon the purely theoretical grounds of difference in the respects mentioned, that the Manila bacillus and other similar bacilli which ferment mannite are not of etiological significance in dysentery. This opinion has now been abundantly disproved by the studies of Flexner and his pupils, who obtained the two types of bacilli from one institutional epidemic of dysentery, and even from the same cases of the disease, and by the investigation of Jürgens of an epidemic of dysentery in Germany in which the mannite-fermenting or Flexner bacillus was alone obtained. Similar results to the last have been obtained by Park in New York.

The confirmatory studies of Marckwald, Müller, Jürgens, and others in Germany, Spronck in Holland, Rosenthal in Russia, Doerr in Austria, Vaillard and Dopter in France, and those of Drigalski in German troops returning from the Chinese Boxer war, leave no doubt of the causative part played by *Bacillus dysenteriae* Shiga in dysentery.

The crucial experiment of producing dysentery in man by the ingestion of cultures of the dysentery bacillus was made by Strong and Musgrave on a Filipino prisoner condemned to death. The immediate result was the appearance of characteristic symptoms of dysentery, from which recovery took place. From the mucoid stools the dysentery bacillus was obtained in cultures. One of my assistants accidentally aspirated into his mouth a small quantity of a fluid culture of the dysentery bacillus, and in spite of thorough and immediate disinfection and lavage of the mouth, a sharp attack of dysentery, followed by recovery, occurred.

The question of difference in the clinical forms of dysentery, depending upon the particular variety or type of infecting bacillus, has not been answered finally. Some writers have held that infection with the original Shiga bacillus tends to cause a more severe set of symptoms than are produced by the Flexner type of bacillus. Park, of New York, has

expressed this view, based upon a small, localised epidemic of the disease in adults; and Charlton and Jehle, pupils of Escherich, have made a similar statement based upon studies of certain cases among infants. My own studies do not bear this out; but I do not think that at present sufficiently accurately collected data exist upon which to decide finally this matter. I have seen, in the same epidemic, cases of dysentery in adults caused by either bacillary type, and they ran about the same clinical course; and it would be difficult to establish severer forms of lesions of intestine than those in Manila from which I cultivated the original mannite-fermenting dysentery bacilli. As a rule, however, dysentery seems to be caused by one type or the other; the occurrence of cases caused by both in a given outbreak of the disease would appear to be exceptional. That mixtures of types may, however, occur in the same individual has already been pointed out; and the collective investigation of diarrhoeas in children by the Rockefeller Institute in 1903 brought out the fact that this mixture of types is true, not only for the "Shiga" and "Flexner" types of bacilli, but also for the "Shiga" and subsidiary mannite-fermenting varieties of the organism. Knox and Schorer have published a series of cases in children, studied at the Wilson Sanatorium, Baltimore, from which they draw the conclusions, first, that in children no relation exists between the types of infecting dysentery bacilli and the clinical course of the disease or the lesions of intestine as revealed at autopsy; and secondly, that the mixtures of bacilli may involve any two or even more of the recognised varieties of the micro-organism. The studies made by the Rockefeller Institute, and the more recent ones of Torrey, and Knox and Schorer, all tend to shew that in children the infecting bacillus is most frequently one of the mannite-fermenting species.

An advance in the knowledge of the dysenteric bacillary diseases has been made by the discovery of Duval and Bassett that the summer diarrhoeas, so called, which prevail in warm temperate climates are frequently caused by the dysentery bacillus. A considerable number of children suffering with this disease has now been investigated bacteriologically, chiefly under the auspices of the Rockefeller Institute, and separate studies have been made by the Health Department of the City of New York and private investigators in several cities in the United States. From 50 to 98 per cent of successful cultivations of the dysentery bacillus from the stools and intestinal mucosa of children were secured. That the winter diarrhoeas of children are associated in a similar manner with the dysentery bacillus is shewn by Wollstein's confirmatory studies at the Babies' Hospital in New York City. These studies in children have brought convincing evidence of the occurrence of single and multiple dysentery bacillus infections. The rule is not yet established for the types of infection most frequently met with, except that the mannite-fermenting bacilli are more commonly found than the Shiga type. Which of the mannite fermenters is the prevailing micro-organism has not yet been determined. The results obtained by Duval and Schorer in

New York in 1903 shewed great preponderance of the Flexner type of bacillus. Of seventy four children yielding the dysentery bacillus seven shewed the Shiga type of organism, in eleven, it existed alone, and in six in association with the Flexner bacillus. They conclude that "single infection with the Flexner type of bacillus is most common, single infection with the Shiga type of bacillus is far less common, and double infection with both organisms is least common in the diarrhoeal diseases of children."

It is exceedingly doubtful whether these conclusions will be found to hold for a larger and more varied material, and already there are indications that they cannot be generally applied. Knox and Schorer's studies at the Wilson Sanatorium in 1905 brought out the interesting point that the mannite-fermenting sub-type of bacillus may occur even more frequently than the Flexner bacillus, and that infections with two or more types of bacilli are more numerous than infection with the Shiga type of bacillus alone.

The intestine contains such a large and varied bacterial flora that other unusual bacilli must be expected to appear in certain cultures from dysenteric cases; and hence it is not surprising to find that certain other bacilli not yet classified have excited the attention of students of dysentery and diarrhoea. Of all these bacteria two groups only deserve at this time special mention—a dysentery-like bacillus which ferments many sugars, including lactose, without the formation of gas, and coagulates milk, and a bacillus acting merely on dextrose, but producing much alkali in milk and other culture media. The first approaches the Flexner, and the second the Shiga type of dysentery bacilli. None of the established dysentery bacilli ferment lactose, and as this lactose-splitting bacillus has not been proved to bear direct relation to intestinal disease, it should for the present be discarded entirely. The same is true of the "alkaline" bacillus, which resembles in some features, but is not identical with, Petruschky's bacillus. Duval and Schorer first drew attention to these bacilli in children, and Torrey and Knox and Schorer have described them in greater detail. Torrey proposed to call them pseudo-dysentery bacilli—a manifestly ill-chosen term, for, as they probably are mere saprophytes, they should not be dignified by a name that can only be misleading.

There can be no doubt that the discharges do not, as a rule, contain the bacilli of dysentery in such numbers or combinations as make it possible to recover them as readily or in as large numbers as from the intestinal mucosa. This was my experience in tropical dysentery, as Vedder and Duval's as regards asylum dysentery, and was further confirmed by Duval and Bassett, and Wollstein and Dewey. It is interesting to note that gentle scraping of the rectal mucosa during life will yield material from which the dysentery bacillus may be recovered when it has not been isolated from the natural intestinal discharges and the most constant results are obtained from deeper scrapings of the mucosa of the intestine *post mortem*, the autopsy having been made soon after death.

The intimate relationship of the bacillus of dysentery to the substance of the mucosa of the intestine, in which locality, under pathological conditions at least, it seems able to survive and multiply, is of considerable significance; and the reverse observation, which shews that this organism increases far less readily and is quickly overgrown in discharges when once outside the body, can be interpreted as indicating that it is less well adapted for a saprophytic than for a parasitic existence.

The collective investigation carried out by the Rockefeller Institute in 1903 shewed the wide distribution of the bacillus of dysentery. The natural habitat outside the body of the micro-organism is not known, and since its mode of entrance into the intestine is still doubtful in many instances. The bacillus has not yet been found in our surroundings, and is known only as occurring in the intestine and very rarely elsewhere in human beings. What is known of its pathogenicity, as obtained from a study of outbreaks of dysentery in adults, would lead us to suppose that it led a parasitic existence in the body of human beings, was not one of the intestinal saprophytes, and gained entrance into fresh human hosts through some mediate agency, such as water, directly contaminated by an infected person. We are, however, confronted by the extraordinary observation that the dysentery bacillus can be found in almost all children who suffer from diarrhoeal disease, in many of whom the symptoms are slight and transient, and clinically of almost no consequence. Moreover, this diarrhoeal affection does not present the appearance of an epidemic disease, least of all of a water-borne epidemic disease, which might account for the great prevalence of the bacillus. It arises throughout the warm months of the year chiefly, in fairly regular succession, and without any indications of explosive violence. A point of difference in the mode of spread of the adult and children's infections is at first sight apparent. While the former often extend with epidemic severity, the latter do not present the features of a spreading epidemic. The cases in children seem to be examples of individual inoculation, although Bassett has described examples of contagion from child to child. This last occurrence can be compared with sporadically communicated infections sometimes seen in institutions containing many aged and decrepit inmates, and possibly with the endemic disease in the tropics, which flourishes less as an epidemic than as a sporadic disease, arising in the many cases from a common source of occasional infection.

That children are also subject to infection during the prevalence of epidemics of dysentery is established. There is little resemblance to the condition found in epidemic diarrhoeas and in epidemic dysentery among children except in the nature of the infecting bacilli. The disparity in the clinical course and morbid anatomy would stamp them as wholly distinct and independent diseases were it not that the same pathogenetic, causative micro-organism has been found to occur in both classes of cases. In morbid anatomy the diarrhoeal diseases are far from forming a unit, while epidemic dysentery in adults and children is usually pseudo-membranous or diphtheritic form of inflammation.



The results obtained by the American investigators of the diarrhoeal diseases of children have not always been confirmed by European investigators. Charlton and Jehle, who cultivated dysentery bacilli of the Shiga and the Flexner type from children suffering either from dysentery or what they regarded as a form of food poisoning, failed to find either bacillus in a group of children presenting the symptoms of summer diarrhoea. This discrepancy has not yet been cleared up. Negative results are, however, at best suspicious in comparison with positive ones, and hence it must still remain doubtful whether this last group of cases should be regarded, as Charlton and Jehle are disposed to consider them, as colon bacillus infections.

It has, of course, occurred to all investigators of the pathological conditions supposed to be due to the dysentery bacillus to search for the dysentery bacillus in healthy persons. The common experience has been failure to find it among the intestinal bacterial flora. The common occurrence of the bacillus in children suffering from diarrhoea necessitated renewed and painstaking search for the organism in healthy children. Duval and Schorer were able, by examining the stools of two healthy, milk fed infants to whom cathartics had been administered, to isolate a few colonies of the Flexner bacillus. The Flexner type has been obtained from two healthy children by Charlton and Jehle. Wollstein also cultivated small numbers of this bacillus from three children not supposed to be suffering from diarrhoeal disease, but at autopsy the intestines showed inflammatory lesions in all. The unexpected finding of the dysentery bacillus in healthy children opens up a considerable field of speculation upon the real pathological significance of the organism. It would seem as if we had no grounds for denying it, in many pathological cases, significance. The presence of the agglutination reaction, the increasing number of organisms in the discharges, the close relationship of the bacilli to the intestinal mucosa, afford ample proof of pathogenetic action. Admitting the possibility that the bacillus of dysentery is after all an occasional, perhaps a constant, inhabitant in some parts of the intestinal canal, where it survives saprophytically among the other intestinal bacteria, it might be considered whether repeated and extensive damage to the intestinal mucosa or functions may not allow the freer growth of the organism, and eventually the acquisition of parasitic and invasive properties.

There is reason to believe that in certain instances in which a species of micro-organism is constantly, perhaps even normally, present in the body in a non-virulent condition, the importation from without of a highly pathogenetic example of the same species ushers in an infection with this micro-organism. It is necessary in such cases to distinguish between auto- and extra-infections with the given parasite. This was seen to be required in some cases of lobar pneumonia, especially in connection with the relatively rare institutional epidemics of the disease. And there is evidence that the cholera spirillum, the typhoid bacillus, the tubercle bacillus, the diplococcus of epidemic meningitis, as well as the pus cocci, may all occur occasionally or constantly in the body as har-



less saprophytes. That the epidemiology of the dysenteric disease will be greatly influenced by the knowledge of the wide distribution of the Shiga bacillus is evident.

Dysentery as a terminal disease in adults the subject of chronic Bright's disease, cirrhosis of the liver, and chronic heart disease would appear from my observations to be of bacillary origin. In several such instances *Bacillus dysenteriae* was obtained in cultures; and Howland has drawn attention to a similar terminal infection with *B. dysenteriae* in children the subject of wasting diseases.

The length of time during which the dysentery bacillus may survive in the intestine is still undetermined. That it can persist there for many weeks, after partial or complete recovery from dysentery, is certain. In an American soldier, invalided from Porto Rico for dysentery contracted during the Spanish War, I shewed that the bacillus survived in the intestine, and produced relapses, for many months. Lentz and Drigalski both speak of relapses of dysenteric symptoms with reappearance of the bacilli in the stools; and Conradi obtained the dysentery bacillus from five children who had entirely recovered from acute dysentery and whose stools had become normal, and from a convalescent four weeks after his illness. Ruge describes the case of a soldier completely recovered from an attack of dysentery acquired in the Döberitz epidemic, who, on returning to his home, suffered from slight looseness of the bowels, and became the source of infection for a small local outbreak of dysentery. That the convalescent and the slightly ill may be carriers of dysentery bacilli must be taken into account in establishing the epidemiology of dysentery, and may serve to explain many of the outbreaks of dysentery which occur in localities and under conditions in which large numbers of persons are closely assembled, such, for example, as public charitable and reformatory institutions and army camps.

**Morbid Anatomy of Bacillary Dysentery.**—The character of the intestinal lesions produced by the *Bacillus dysenteriae* is very variable. Any analysis of the lesions must first deal with the widely diverse conditions met with in adults the subjects of the epidemic, endemic, or sporadic infection, and in children suffering from epidemic or true sporadic dysentery, and presenting the more diverse symptoms and lesions of so-called summer diarrhoea of warm countries.

The most definite diseases, as based upon morbid anatomy, are the epidemic and endemic dysenteries proper, which may be acute or chronic. In the acute disease the intestines present catarrhal, pseudo-membranous, and ulcerative lesions. The catarrhal process may, in very mild examples of the disease, be alone present; it is, as a rule, associated with the other more severe lesions of the disease, which affect a much smaller part of the intestinal canal than it does. While the diphtheritic and ulcerative effects are usually limited to the large bowel, the catarrhal process may include as well more or less of the small intestine. The intestinal catarrh is not peculiar to dysentery, and does not, therefore, call for special description here. Since these pathological changes

are initiated, if not caused wholly, by one species of micro-organism, their description should follow not as separate diseases but as different manifestations of the same disease.

Dysentery in adults and the epidemic and rarer sporadic disease in children shew the same kinds of pathological changes in the intestine. The peritoneal cavity is relatively normal in appearance; but on close inspection an undue turgidity of the blood-vessels of the large intestine may be noted, and more rarely the vessels of the lower part of the ileum are also injected. The mesenteric lymphatic glands, especially those of the rectum and sigmoid flexure, are hyperæmic and swollen, while the glands placed higher up in the abdomen shew less swelling or are entirely unaffected.

The appearance of the small intestine varies. The mucosa may be pale and the contents normal in appearance; or there may be increase in quantity of the contents. In many, but not in all, cases the small bowel escapes more serious lesions. But in severe cases, and especially in the severe epidemics and in endemic tropical dysentery, the small intestine is the seat of hyperæmia, oedema, sometimes even of hæmorrhage and the production of false membrane. The lower part of the ileum is the part of the small intestine most frequently involved, although Peyer's patches usually escape; the solitary glands may be swollen and hyperæmic, though they are rarely ulcerated, thus contrasting with the frequency of ulceration of these nodules in the large intestine.

The lesions of the large intestine are also extremely variable, but the more characteristic ones make up the classical pathological picture of dysentery. The descriptions given by Virchow in several papers, especially in that dealing with the dysentery of the troops returning from the Franco-Prussian War, leave very little room for additions. The character of the lesions depends upon the stage of the process, and it is usual to divide the disease, upon clinical and pathological grounds, into acute and chronic stages.

It has been customary, since Virchow's descriptions, to look upon the intensity of the lesions in the colon as depending upon the length of time the fæces, supposed to carry the injurious agents, remain in contact with the mucous membrane. Hence the flexures of the colon, the cæcum, and the ampulla of the rectum usually shew more severe and advanced lesions than other parts of the large gut. This rule is, however, not without important exceptions, and some writers have drawn especial attention to the affection of certain segments of the gut. For example, the rectum, sigmoid flexure, and ileo-cæcal valve are stated to be most often the seat of the disease in Cochin China, while in the Antilles and in the French Sudan the transverse colon is believed to be attacked first, the rectum becoming affected later. My observation of the endemic bacillary dysentery of the Philippines led me to conclude that in the severer cases the mucosa of the whole of the colon suffered uniformly, and this is confirmed by Strong and Musgrave.

The acute lesions are first seen on the elevations of the folds of the

mucosa; from these localities they extend to the lower levels. The lesions consist of swelling and necrosis of the mucous membrane, with pseudo-membrane formation. The surrounding mucous membrane is hyperæmic and cedematous, often hæmorrhagic, and covered with mucus of a glassy appearance, which is often blood-stained. This material has been compared by Ziegler to white of egg. Later on, the pale colour of the pseudo-membrane alters, and becomes a darker greyish-green tint. The false membrane does not extend uniformly and continuously, but spreads out irregularly and from separated islands of deposit. The result is an irregularly figured, elevated, whitish or discoloured pseudo-membrane surrounded by deeply congested mucous membrane. The consistence of the wall is increased by reason of the infiltration of the mucosa and submucosa. As has been mentioned, the solitary lymphatic glands become enlarged and sometimes soften and ulcerate in the centre.

Ulceration of the mucosa is common in this stage of dysentery. It is brought about by the separation, by means of localised inflammation, and possibly through the agency of secondary invading micro-organisms, of the necrotic mucous membrane and false membrane. The ulcers, therefore, depend in superficial extent and depth upon the degree of previous necrosis. Not infrequently adjacent areas of necrotic membrane are separated and cast off, thus giving rise, by continuity, to large ulcers. Hence the great variation in size, form, and depth. The ulcers usually present a clean surface, the edges are generally elevated, and the base may be formed by the submucous or even by the muscular coat; the ulcers are rarely confined to the mucous membrane. Exceptionally all the coats of the intestine are involved in the destructive process and the serosa is perforated. By reason of this continuity of extension large areas of the gut may be undermined, and sloughs of the tissue of corresponding size may be separated and be passed in the motions, or, if imperfectly separated, may be found adhering to the ulcers. When ulceration penetrates deeply, inflammation of the peritoneum often sets in and leads to localised exudate upon the serosa, and also, at times, to adhesion to neighbouring loops of intestine. These localised inflammations may eventually give rise to permanent thickening of the gut and to pathological adhesions and kinks. Actual suppuration of the mucosa never occurs in uncomplicated cases of bacillary dysentery. When much pus is present in the exudations, large numbers of pyogenic cocci—streptococci chiefly—will be found to be present.

The process of repair may begin at any stage of the disease and progress to complete restitution of the intestine, or to such partial restitution as, while restoring largely the integrity of the mucosa, leaves the submucous, muscular, and peritoneal coats permanently altered by cicatrization. Even the mucosa is altered by the new tissue which leads to puckering of its surfaces and modifies the glandular structure.

In the chronic disease the whole intestine is thickened, indurated, more or less narrowed with corresponding dilatations above the strictures. The serous membrane covering the thickened loops of intestine may be

pigmented. The surface of the mucosa is often dull in appearance, and pigmented depressed areas—the scars of healed ulcers—are often present. The pigmentation extends, at times, into the adjacent normal mucosa. Islands of mucous membrane, separated by depressed scars, often persist, and by cicatricial contraction are thrown into undue prominence, in this way areas of mucosa, partly strangulated by scar tissue, may give the surface of the intestine a polypoid appearance.

The full etiology of the chronic forms of dysentery which succeed a small proportion of cases presenting at the outset acute symptoms has not yet to be worked out. The probability that mixed and perhaps multiple infections have occurred is a strong one. That the pyogenic cocci play a part in bringing about the final results seems likely; and the colon bacilli may even not be wholly innocuous as the blood sometimes shews agglutination for them. In keeping with this long period of intoxication the wall of the intestine sometimes shews amyloid change. Unless reinfection has taken place, acute lesions, such as hæmorrhage or the formation of false membrane, are absent. But exacerbations are so common that it not infrequently happens that small extravasations of blood and areas of necrosis and false membrane co-exist with the scars of a more ancient disease. Should separation of the necrotic tissue have occurred then recent ulcerations may be present also. It is not rare to find the several stages of the disease existing side by side, but in the chronic disease the acute lesions are, as a rule, subordinated.

The *microscopical appearances* vary with the stage and intensity of the disease. The characteristic histological changes are found, in the acute disease, in the mucous, submucous, and muscular coats, and are most marked in the first situations. It is impossible, in a brief space, to cover the varying microscopical appearances, and hence a description of the severer lesions only will be given.

The changes of the mucous membrane consist of coagulative necrosis with exudation of fibrin and polymorphonuclear cells. The fibrinous and cellular exudate may entirely replace the glandular layer, in the affected parts, or here and there a gland may be preserved. The pseudo-membrane is a close-meshed network of fibrin enclosing multinuclear often fragmented, cells. Often no blood-vessels can be distinguished, but a number of red blood-corpuscles are mingled with the exudate and are free upon the surface. The muscularis mucosæ may be lost in the exudate. The chief change in the submucosa is the thickening of the wall of the gut. The part which tends to be most affected is the layer next the muscularis mucosæ. Hæmorrhage, fibrin, and cellular accumulations occur there in irregular distribution. In the deeper parts the cellular infiltration is less, but oedema, fibrin, and hæmorrhages are correspondingly increased. The exuded white corpuscles consist chiefly of Urmann's plasma cells, which are collected into foci, often about veins and arteries; but they occur also singly and in small groups. A variable number of polymorphonuclear, neutrophilic, and eosinophilic cells are also present.

The inflammation in the deeper parts of the intestinal wall extends

ally beyond the limits of the diseased mucous membrane, and in the mucosa the exuded cells may intermingle with lymphoid cells. The blood-vessels of the submucosa may be patent and congested, the blood containing an excess of white elements; or they may shew recent hyaline, and fibrinous thrombi. Hyaline degeneration of the cellular walls does not occur in this stage. Dilated lymphatic spaces contain fibrinous clots. The muscular coat shews a variable cellular infiltration consisting of red and white corpuscles, but the peritoneal surface, as a rule, escapes invasion. When, however, the ulceration has extended deeply into the muscular coat the serous membrane is covered

with a fibrino-purulent exudate, corresponding in extent, more or less, to the area of tissue destruction.

The process of repair consists in the formation of granulation-tissue at the depth and from the sides of the ulcer. Gradually the defect is closed, but the histological regeneration of the several coats is imperfect.

The pigmentation of the scar and adjacent mucous membrane is due to iron-containing blood pigment—hæmosiderin—which reacts with the

contents of the intestine to produce iron sulphide. The appearance of similar pigmented areas in the serous coat follows punctiform extravasation of the blood into this membrane.

These follicular ulcerations are frequently the results of suppuration of the dilated crypts of Lieberkühn.

Bacteria are abundant in the fibrinous exudation in the mucous membrane, and consist of cocci and bacilli. In specimens stained by Gram or Weigert's methods, large numbers of cocci, in short chains or pairs, can be seen. Other specimens, stained in alkaline methylene blue,

beside cocci, many bacilli of the colon-typhoid-dysentery bacilli are seen.

Microbiology. The bacteria are abundant in the necrotic mucous membrane, but they are less easily found in sections in the deeper tissues.

Adjacent preserved glands often shew bacilli, which may be discovered in the submucous and muscular tissue, but less often than might be expected. There is no means of distinguishing the dysentery bacillus

micrologically from other intestinal bacilli of the same group.

While bacillary dysentery in adults is a disease possessing a fairly characteristic morbid anatomy, and while epidemic dysentery in children agrees

in symptoms and in morbid anatomy with that disease of adults, the sporadic bacillus infections in children, which arise sporadically and

usually in warm climates, present the greatest variety of symptoms and lesions.

Howland has studied the gross and microscopic changes in the intestines of two children, in all of whom the dysentery bacillus (Flexner type) was present, and he concluded that all grades and types of disease, as

described by clinical symptoms and pathological lesions, are met with in this group of cases pseudo-membranous inflammation occurs; in another

group the intestinal mucosa escapes, while hyperplasia of the lymphatic glands, both agminated and solitary, with, in some instances, denudation

of the superficial epithelium and "pitting" of the follicles, exist; in a third group superficial necrosis and ulceration of the mucosa, not limited



to the follicles and independent of false membrane, take place; while the fourth group, which includes the largest number of cases, shews few or no lesions either to the naked eye or under the microscope.

**Experimental Dysentery.**—The lower animals, after being fed on the *Bacillus dysenteriae*, do not develop the symptoms or lesions of dysentery. The dog, which may succumb to simple feeding on cultures, develops diarrhoea, and after five or six days, in fatal cases, the mucous membrane of the gut may shew hyperæmia and small hæmorrhages. From the mucus, which is in excess, the bacillus may be recovered in cultures. Cats are insusceptible to cultures given by the mouth unless preceded by croton oil, in which case the diarrhoea may persist, the bacilli be recovered from the dejections, and, finally, death may result. The lesions are not characteristic. Lower monkeys are not affected by large quantities of cultures, even when preceded by croton oil purgation. On the other hand, almost all animals respond with swelling and illness to subcutaneous injections of the cultures, whether alive or killed at a low temperature. If the dose of bacilli given be large they may succumb. Mice and guinea-pigs are relatively susceptible to intraperitoneal injections of living and dead cultures. The lesions are inflammatory and not specific.

In striking contrast to the absence of characteristic appearances in the animals mentioned is the rabbit, which is peculiarly sensitive to certain strains of the dysentery bacillus, and reacts in a manner which much more closely resembles the natural dysenteric disease in man. If cultures of the Shiga type of bacillus be injected into the rabbit—under the skin into the abdomen, or intravenously—diarrhoea develops in a fair percentage of animals, and usually ends fatally. Lesions appear sometimes in the small intestine, sometimes in the large intestine, sometimes in both at the same time. The small intestines are dilated and filled with soft, yellowish fæces, and the Peyer's patches are swollen, and punctiform hæmorrhages occur in the mucosa; the lesions in the large intestine are limited, for the most part, to the dilated cæcum, the vermiform appendix, and the colon in the immediate neighbourhood. The walls of the cæcum, which shew the most pronounced lesions, are greatly swollen, œdematous, hæmorrhagic, and the mucosa is often covered with false membrane. Ulceration occurs in animals surviving a few days. The lymphatic tissue of the cæcum at its junction with the ileum, and of the vermiform appendix, is greatly swollen. The pathological appearances presented by the cæcum resemble in many ways, acute pseudo-membranous dysenteric lesions in man.

It has been shewn that the lesions result from the action of a toxic substance, since they occur from the injection of filtrates obtained from the Shiga bacillus as well as from the bacilli themselves. The susceptibility of the rabbit to this toxin is very high;  $\frac{1}{100}$  of a cubic centimetre or even less of a filtrate obtained from an autolysed culture sufficing to produce the lesions and cause the death of the animals. Vaillard and Dopter have described similar ulceration of the intestine in dogs to whom



the dysentery toxin was given. Feeding animals with the toxin or cultures of the bacilli has no visible effects on the intestinal mucosa.

Rabbits also suffer from paralysis of the extremities, due to inflammation of the grey matter of the spinal cord, from intoxication induced by the Shiga bacillus.

As the result of an investigation into the pathogenesis of the intestinal lesions in rabbits, Sweet and I concluded that the lesions are eliminative in character. Since they arise only when the toxin reaches the intestine with the blood, it is to be presumed that they depend upon excretion of the poison by the intestine. We found, moreover, that the toxin is eliminated into the intestine, in large part, apparently, with the bile, and that the presence of a biliary fistula in the rabbit prevents the development of the intestinal symptoms and lesions, although the animal still succumbs to the neurotoxic poison. The toxin is, doubtless, reabsorbed in its passage through the small intestine, the elimination being gradually effected, chiefly by the cæcum, and in this way lesions arise. Direct application of a powerful toxin to the mucous membrane of the small intestine, or to the cæcum, partly emptied of its contents by purgation, does not lead to inflammation, necrosis, or to the production of false membranes.

It is not improbable that in man the intestinal lesions of dysentery have a similar origin. The dysentery bacilli multiply throughout the intestine, but marked damage is mainly confined to more or less special parts of the large intestine. Absorption of the dysenteric toxin from the small, and possibly also from parts of the large intestine, followed by excretion of the poison by specialised areas of mucous membrane, is what may be assumed to occur in man. The influence of the mechanical pressure of the faecal contents in determining the localisation of the lesions becomes wholly of secondary importance, and serves at most to alter the circulation and nutrition at the site of contact, through which either the process of excretion is modified or the injurious action of the poison promoted.

The occurrence of toxic, necrotic, and pseudo-membranous lesions in rabbits shews that the presence of bacteria in the membrane does not suffice to account for the damage to the tissues and subsequent fibrinous inflammation. Since similar results to these are caused by metallic poisoning—especially by mercurial poisoning—the toxic action of certain bacterial poisons on the intestine and of these heavy metals may be viewed as produced in the same manner. In this connexion it may be pointed out that Sweet and I observed that rabbits with biliary fistulae developed much slighter lesions in the cæcum after mercurial poisoning than the control animals.

SIMON FLEXNER.

**Symptomatology.**—1. *Acute Dysentery.*—The incubation-period of true dysentery extends from 24 to 48 hours. In pseudo-dysentery the symptoms follow the exciting cause in from 6 to 12 hours. Dysentery may set in suddenly; sometimes it supervenes on a period of constipation,

but more frequently it begins as diarrhoea which has nothing about it to excite suspicion. During this premonitory period some loss of appetite and general malaise may be complained of. When the looseness has continued for a day or two, defecation begins to be accompanied by griping, commencing around the navel and radiating along the course of the colon. The stools become more frequent, and are passed with uneasiness increasing to straining. The stools now change their character, the faeces of the diarrhoeal stage (if such existed) being mixed with mucus streaked with blood. Blood and mucus soon constitute the entire evacuation, which is preceded by distressing griping pains (tormina) and prolonged and painful straining (tenesmus). The ingestion of food or drink, or movement of any kind, provokes a call to stool, but apart from any such provocation a continual desire to evacuate the bowels is present, which is but momentarily, if at all, relieved by going to stool. Long continued straining results in the passing of a small quantity of bloody mucus, and the smaller the quantity the greater the straining. Occasionally small, hard masses of faeces (scybalæ) are passed. After a few days, the anus becomes inflamed and is the seat of burning pain, bringing on spasmodic contractions, which at a later period give place to relaxation of the sphincter ani, so that prolapse may ensue. When the rectum is much affected the bladder sympathises, and dysuria increases the sufferings of the patient. Pressure in the course of the large intestine often elicits pain. In mild cases, fever is frequently absent or insignificant, and afebrile cases are not always free from danger. It is rare for the fever in uncomplicated dysentery to make its debut by a rigor. When the patient has suffered, or is suffering, from the malarial infection there is often an evening rise of 2 or 3 F. In the more intense forms, fever is present apart from malarial complications. Shiga states that in the dysentery of Japan the temperature often rises to 100° or 102°, and not seldom to 104° F. Drs. Washbourn and Richards observed numerous cases of dysentery in South Africa with irregular pyrexia, reaching 101° to 103° F., starting at the commencement of the attack, lasting from three to eight days, and falling coincidently with an improvement in the stools. In the later stages the pulse becomes weak and fast, the action of the heart rapid, irregular and feeble. The appetite is impaired, the tongue coated, and in some cases a sub-icteric tinge of the skin is observed. Vomiting is generally absent, and is seldom urgent, unless the dysentery is complicated with an inflammatory affection of the liver. The urine is decreased. The urea and uric acid are in excess, the chlorides diminished, and albumin, if present at all, is in small amount, unless in the severer forms of the disease. The blood changes have not been much studied. According to Strong and Musgrave, there is some polymorphonuclear leucocytosis, but this is not seen in rapidly fatal cases. The red corpuscles are at first relatively increased from the drain of fluid from the bowel, but fall below the normal when blood makes its appearance in the stools. The stools, which in mild cases vary from 15 to 50, and in severe cases may number 100 a day, are destitute of fecal odour and consist at first of mucus and

This, at least, is generally the case when the disease is limited to one extremity of the bowel. After a time they assume a serous character. A reddish fluid, mixed with white flakes and small flesh-like particles—the *raclure de boyaux* of French physicians—makes its appearance. This fluid, unlike that of the first stage, is rich in albumin; the daily loss of which in a dysentery of moderate severity has been estimated by Oesterlen at  $1\frac{1}{2}$  or 2 ounces—a drain which accounts for the rapidly increasing emaciation and debility of the patient. The evacuations have a nauseating, the serous ones an offensive odour, characteristic of the disease. The disease may be arrested or prove fatal at this stage, or pass into that of gangrene. Dysentery does not, however, always run its course in distinct stages. The evolution of the disease and the character of the stools vary greatly in different epidemics—more so, in fact, than ordinary descriptions would lead one to suppose. In some of the most dangerous and rapidly fatal cases the stools are more or less present throughout, of a green colour, mixed with blood, at one time containing much mucus, at another consisting of a dark brown offensive fluid. Sometimes, again, there are vomiting of greenish matter and copious bilious stools for the first day or two, mucus and blood appearing later. Sudden changes in the character of the stools indicate danger. Then, it is to be feared that in some fatal cases there is little complaint of tormina and tenesmus. The dysenteric toxin has a marked influence on the muscular and nervous apparatus of the heart, giving rise to functional disturbances, and more rarely to organic disease. Thébaut observed a very infectious outbreak at Vincennes in 1897, in which 42 per cent of the patients had severe functional disturbance of the heart. In some cases there was slight hypertrophy of the left and flaccidity and dilatation of the right ventricle. Nenninger met with numerous cases of functional heart disease among German soldiers convalescing from dysentery contracted in China. The symptoms were rapid, weak, irregular, functional murmurs, dilatation of one or both chambers. The muscle of the heart apparently undergoes degenerative changes in the later stages. Intestinal perforation will be indicated by symptoms of peritonitis, or by those of perityphlitis or periproctitis.

**Gangrenous Dysentery.**—Gangrene may supervene during the progress of the attack, or the symptoms from the commencement may have been of great intensity, the disease rapidly ending in sloughing. One is almost never in speaking of a primary gangrenous dysentery in those cases in which death takes place as early as the third or fourth day. Extensive gangrene has frequently been met with in the epidemic dysentery of warm climates, as in the Glasgow epidemic of 1827-28, in the Glasgow Asylum in the same years, in Edinburgh in 1828, in London in 1859. The diagnostic characters of gangrene are derived from the colour of the stools and the concomitant constitutional disorder. The stools are, of a dark brown colour, mixed with pus, thin membranous shaggy, or black flaky sloughs of the mucosa, or thicker, dark grey, shaggy, crusted sloughs of the mucosa and submucosa, with a grumous

deposit consisting of the débris of the disintegrated intestine mixed with blood and pus. Tubular sloughs are sometimes passed. Sir J. Esdaile records a case in which a tubular slough about a foot long was discharged, and Dutroulau another in which 12 inches of the mucous and submucous coats were discharged. Both patients made a good recovery; favourable termination in these cases is undoubtedly rare. The constitutional symptoms of gangrenous dysentery are those of intense prostration. The pulse is fast and weak; the extremities cold, the tongue dry, red, and glazed, or black; the urine is scanty, and albuminous; occasionally there is suppression.

Towards the end, in all forms of dysentery, the tormina and tenesmus decrease or disappear, the motions pass involuntarily, the tongue becomes dry, the temperature sinks, collapse sets in, and troublesome symptoms announce the end. The mind generally remains clear till the last, in some cases the patient falls into a state of low delirium.

When a favourable issue from the simple or the gangrenous form is in prospect, the motions become more healthy and feculent, and less frequent; the urine is more abundant, the patient's strength and appetite improve, and the pulse, temperature, and tongue become normal. In some forms of dysentery, or pseudo-dysentery, often recover on the third or fourth day, while still in the mucous stage. More severe attacks may last for a week or a fortnight, or even longer. Some cases take a fulminant course and prove fatal in from three to seven days, without gangrene.

Microscopically, the stools in the first stage are found to contain hyaline mucus, mixed with red and white corpuscles, bacteria, and epithelium from the bowel. Fæcal detritus is often absent. At a later stage they consist chiefly of blood and pus, with sloughs, broken-down mucus, and undigested fragments of food. A bacteriological examination in most instances, reveal one or other of the varieties of Shiga's bacilli. In an early stage almost in pure culture, but later mixed with other bacteria. Pathogenetic amœbæ are absent, but mixed infections have been what frequently observed in the Philippines and the United States.

*Chronic Dysentery.*—Chronic dysentery, rarely originating in temperate climates, appears in three ways:—(a) An acute attack, instead of ending in recovery, persists in a mitigated form. (b) After recovery dysenteric symptoms of a milder but more persistent character reappear. (c) The disease occasionally originates in a recurrent form which gradually assumes more and more of a dysenteric character.

In whatsoever way it originates, a looseness, accompanied with more or less colic and straining, is characteristic of the malady. There are periods of quiescence when the motions are healthy, or comparatively so. These are succeeded by exacerbations, during which the calls to stool are frequent; the motions are watery and more or less frequent, mixed with blood, mucus, or pus, or with all three at once, and have the true dysenteric odour, but amœbæ are absent.

When this condition is prolonged, the health of the patient deteriorates.

ates. He becomes weak and anæmic; the appetite is bad, capricious, or ravenous, and digestion is impaired, as is manifested by flatulence and uneasiness after meals, and by the passage of undigested food with the feces.

Stenosis from cicatricial contraction is not a common sequel, and is less often noted now than formerly, but it certainly occurs, and in thirty years' experience I have seen five or six cases where it was present: the abdomen becomes tumid and tender, the feeling of distension is distressing, flatulent eructations and paroxysmal attacks of colic occur, the breath acquires a feculent odour, and the evacuations are scanty and voided with difficulty. Towards the end, the pulse fails, the tongue becomes red and glazed, vomiting and night-sweats occur, œdema of the feet sets in, and the patient, after months or years of suffering, dies of exhaustion, or is carried off by some intercurrent disease.

*Dysenteric Diarrhea.*—The frequency with which dysentery and diarrhea have occurred simultaneously in barracks, among men living under the same conditions, gave rise long ago to the inference that dysentery may run its course as a simple diarrhea. This inference has been confirmed by the isolation of Flexner's bacillus from the stools of an epidemic intestinal catarrh recently observed in West Prussia, which later developed the symptoms of clinical dysentery. We have thus to recognise a dysenteric diarrhea. This disease is most prevalent in large cities in America during the summer months, in children under three years of age, and especially in those brought up on the bottle. It is most common in the poorer insanitary quarters of a town, and is not infrequently met with in hospitals and other institutions where numbers of children are congregated. Although it is rare for more than one child in a household to be attacked, several instances are on record of its spread in institutions. It occurs as an acute disease of sudden onset in children previously healthy or more insidiously in those suffering from malnutrition and digestive disturbances, and also as a terminal infection in pneumonia, bronchitis, measles, scarlet fever, and other diseases.

The symptoms in the milder forms are those of a simple diarrhea with little or no fever. The stools— from four to ten daily—are yellowish or green, mixed with mucus, sometimes streaked with blood, and passed without tenosmus worth mentioning. Clinically, it is a diarrhea, its relation to dysentery being indicated only by the presence in the stools of Flexner's, occasionally of Shiga's bacillus.

The severer forms present more of a dysenteric character, the stools being somewhat more numerous, but seldom exceeding ten to twenty in twenty-four hours. They are thin or watery, yellow, green, or brown in colour, contain mucus and generally streaks of blood, and are passed with more or less griping and tenosmus. When the disease occurs in a previously healthy child it often begins with vomiting and fever. The temperature ranges from 99 to 104 F. Tympanites, restlessness, emaciation, prostration, and coldness of the extremities appear during the course of the disease in its graver forms. Death occurs most frequently within



the first ten days, but many cases run a course of several weeks, and recover gradually or succumb to exhaustion or some intercurrent disease.

A severe epidemic form of infantile dysentery, met with in Japan, has been described under the name of "*Ekiri*." It begins with a violent fever and dysenteric stools, without tenesmus, and often terminates with cerebral symptoms. The case-mortality is 30 to 50 per cent. It seems to be caused by a special bacillus.

*Modified and Complicated Dysentery — Malarious Dysentery.*—When associated with mild malaria the only peculiarity to be observed in most cases of dysentery is an evening rise of temperature of from 1° to 3° F. When occurring in a patient who is labouring under an intense malarial infection, dysentery usually assumes an aggravated type, affecting principally the cæcum and ascending colon, and tending to prostration and algidity. When algidity is early and marked the malarial element is almost always predominant. A form of dysentery attacked the fever-stricken troops in Mauritius in 1866-67, after they had been removed to a non-malarious island off the coast. Power, who described it, says, "The stools were a smoky, dark fluid, consisting of disintegrated blood and water. No sloughs until some time after the commencement of the disease, and not necessarily then. There was no trace of feculent or, indeed, of any solid matter. There was great depression with a tendency to coldness of the body, but the mind remained quite clear. After death either total sloughing of the internal coats of the large intestine or merely a prominent state of all the glands was observed."

Yet another condition has been observed associated with malaria, in which the patient is free from intestinal symptoms during the apyrexial intervals, while during the febrile paroxysms he passes large quantities of liquid blood, pure or mixed with fæces. In some instances this magma of blood and fæces was observed by Bérenger-Féraud to amount to three litres in two hours.

*Scorbutic Dysentery* is chiefly marked by its insidious onset, its dangerous character, and by the large amount of sanguineous fluid, mixed with mucus, shreds, and sometimes sloughs passed in the stools, which retain their feculent character. The outbreak at the Millbank Penitentiary was of this kind.

Dysentery when associated with typhus often assumes a malignant character, and is extremely infectious. Relapsing and enteric fevers are often associated with the dysentery of war and famine.

The *Caribi sickness* of Guiana, known as *el Bicho* in Brazil, the *mal de valle* in Ecuador, *Bischeo* in Trinidad, which is probably similar to, if not identical with, the epidemic gangrenous proctitis of Fiji, appears from time to time in destructive epidemics. Hartle describes the *Bischeo* of Trinidad as "ushered in by pyrexia and the most malignant concomitant symptoms of the malady, by profuse hæmorrhage from the bowels and extreme relaxation of the sphincter ani. In some of the cases the tenesmus was distressing, in others there was no pain whatever; yet



the blood was constantly streaming from the rectum, while the anus tremely dilated."

*Arthritic Dysentery.*—In some outbreaks of dysentery, as that at Caen in 1850, at Bloomfield in Ohio in 1851, in Norway in 1859, and at Döberitz many in 1901, arthritis is a rather frequent concomitant or sequel of dysentery. The large joints are affected, especially the knee, ankle, and wrist. The heart is seldom involved, and, as a rule, the disease, although severe, is not dangerous. Those who are hereditarily disposed to rheumatism, or who have already suffered from it, are not more liable than others to be thus affected.

*Septic and Pyæmic Complications.*—The absorption of noxious matters from the bowel occasionally produces in dysenteric patients nervous depression, sleepiness, and low delirium. The tongue is black, the pulse is rapid and fast, and the patient dies of septic intoxication. Pyæmic complications, with recurring chills, parotitis, diffuse abscesses, or peritonitis, are occasionally met with.

*Liver Complications.*—Mild cases of dysentery everywhere, and even severe cases in temperate climates, generally run their course without appreciable sign of liver complication. In the majority of cases in tropical climates, however, whether terminating favourably or fatally, this organ is more or less implicated. In a certain number of cases, signs of liver trouble precede, by some time, the dysenteric disorder; in other instances the liver and bowel are simultaneously affected, congestion of the liver declaring itself during the progress of the dysentery, and frequently enough after a rather temporary diminution in the number of the stools. Pain or a sense of fullness in the right hypochondrium, increased on deep pressure, accompanied or not by a slight rise of temperature, a slight enlargement of the liver, with nausea or vomiting, and occasionally a certain degree of jaundice, mark the presence of a congestive liver complication. When these symptoms are followed by a rigor, or accompanied by a distinct outbreak of fever and hepatic symptoms, the formation of an abscess may be expected, but this termination is comparatively rare in bacterial dysentery, although it does undoubtedly occur.

*Relapses and Sequels.*—Relapses are prone to occur after exposure to cold and indiscretions in diet up to ten weeks, or even more, after convalescence, and are more commonly observed in persons enfeebled by the use of alcohol. The bacillus of dysentery reappears in the stools during a relapse.

Sequels are seldom observed after mild seizures. After more severe attacks paralysis of the lower extremities, of the sphincter ani, or of the bladder have been observed. Troubles of digestion, hepatic disorders, hemorrhoids, prolapsus ani, irritation of the bladder, cystitis, nephritis, oedema of the legs may also be reckoned amongst the sequels of the disease—disorders of the digestive functions being the most common.

*Dagnosis and Prognosis.*—A careful study of the symptoms of the disease, along with an inspection of the stools and an examination of the

abdomen (which should never be omitted), will suffice to guide the practitioner to a correct diagnosis. In doubtful cases the bacillus may be isolated from the stools in the earlier stages of the disease. The agglutination test is generally negative for the first six or seven days, but it may be resorted to with advantage in order to distinguish the bacterial from the amœbic form of the disease. The *prognosis* must depend partly upon the nature of the epidemic; upon the prevailing type of the disease; the character of the stools, their frequency, the presence or absence of sloughs or of a gangrenous odour; upon the presence and degree of fever; upon the site and extent of the process, the danger being greater when the disease is seated in the cæcum and ascending colon, and still more so when the whole of the intestine is invaded, and, finally, upon the extent to which the constitution is affected by the local disease. Hiccup occurring in the later stages, great nervous prostration, low delirium, a decrease of the tormina, accompanied by increasing debility, inflation of the abdomen, and algidity are all of evil import.

The *prophylaxis* of dysentery must be deduced from its etiology. The resident, in countries where the disease is endemic or epidemic, should see that the soil in the neighbourhood of his dwelling is maintained free from faecal pollution. The purity of the water-supply should be carefully looked after, and if there be the slightest reason for suspicion on this point the water should always be boiled before use. This precaution should never be neglected by travellers in tropical regions, where all water should be looked upon as suspect, and treated accordingly. Above all, surface-water should be avoided. Food should also be of good quality, well cooked, and excess and defect alike avoided. The use of uncooked vegetables, fruits, and salads, even when washed, is not free from danger in countries where dysentery prevails. Alcoholic stimulants, if used at all, should be taken in strictest moderation. Diarrhoea and constipation alike should be guarded against. Wet and cold, especially after exposure to the tropical sun and great fatigue, must be avoided as far as practicable. When the clothes get wet, whether by perspiration or rain, they should be changed as soon as possible. The cummerbund or abdominal belt of flannel should be used in the tropics. Dysenteric stools must be disinfected and disposed of by covering them deeply with earth at a distance from the dwelling. In camps they should be disinfected immediately and then disposed of by cremation. Bed-pans, commodes, enema syringes, and bedding should be thoroughly disinfected. Redoubled attention to these precautions is to be enforced when the disease is epidemic. The prophylaxis of famine dysentery is largely a matter of state policy; that of war demands the prevention and avoidance of the remoter causes of the disease. The Japanese ascribe their comparative exemption from dysentery during the Russian war to their practice of sending on in advance sanitary officers to test the purity of the water in the country to be traversed, and to indicate the sources that could be safely used by the troops. Prophylactic serums appear likely to be of very limited application (cf. p. 524).

**Treatment.**—Experience teaches that one kind of treatment does not answer in all forms of dysentery, nor will one drug suit all stages of the disease. Dr. Clouston, in an outbreak of dysentery occurring in the Cumberland Asylum, tried the ipecacuanha treatment in every possible way—by mouth and rectum, in doses from ten grains to a drachm, alone and in combination with opium—without success. In the malarious dysentery mentioned above, which attacked the troops in Mauritius in 1866-67, ipecacuanha was not of the slightest use; but the disease seemed to yield to large doses of the tincture of the perchloride of iron. The form of dysentery that attacked the inmates of Millbank Penitentiary in 1823-24 resisted blisters, bleeding, fomentations, and the use of astringents, bitters, aromatics, and ipecacuanha that were tried in succession. The one remedy that proved of real value was mercury, in the form of grey powder or calomel, which, as Latham says, was given at last with the greatest apprehension after all other medical expedients had failed. In some cases in which the tormina and tenesmus were extreme, and the evacuations extremely frequent and consisting entirely of blood or morbid secretions, fifteen grains of calomel and two grains of opium were given, and afforded marked relief. Mayne also states that he and his colleagues found mercury to be “the principal remedy” in the dysentery which prevailed in the South Dublin Union Workhouse in 1848-49. This is what one would scarcely have expected in famine dysentery. Among more recent authorities, Trousseau and Brenger-Féraud—the experience of the former being limited to France, that of the latter to the French tropical colonies—attest the value of mercurials in some of the severe forms of the disease. Niemeyer considers the administration every two hours of one grain of calomel, with quarter of a grain of opium, to be the “most trustworthy treatment” in the higher grades of dysentery. Scheube, from his experience in Japan, recommends calomel in doses of  $7\frac{1}{2}$  grains every four to six hours, with castor oil to obviate constipation. On an average he found 45 to 60 grains sufficient to effect a cure. Plehn also prefers calomel in the dysentery of West Africa, but gives it in doses of  $\frac{1}{2}$  grain hourly by day only for three days, preventing constipation by castor oil or by enemata of salicylic acid, and allaying salivation by gargles of rhatany. After three days of calomel treatment he resorts to bismuth. I have given these experiences somewhat in detail, because I am about to recommend a different treatment, warranted by my own experience and that of others in tropical countries. If it be true, as I believe it to be, that more than one morbid state is included under the name of dysentery, we shall be prepared to find that the treatment adapted to one form or stage may not be useful in another. The physician, therefore, should not allow doctrinal prejudices to prevent him from having resort to remedies which have been found life-saving in certain forms of the malady.

The chief point, however, in all forms of dysentery alike is the hygienic and dietetic treatment, and many of the milder cases yield to

this alone. Rest in this disease is an important curative agent. patient should be put to bed at once. The room should, for obvious reasons, be well aired and free from draughts.

In many cases the patient will feel relief from the application of a linseed-meal poultice, large enough to cover the whole abdomen, belly and sides, and changed before—not after—it begins to get hard. Care must be taken that the patient is not exposed to chill, and that the bed-clothes are protected from damp. If there be considerable irritation, a sinapism or spongio-piline placed in hot water and sprinkled with turpentine will be of service. Cases occur in tropical countries in which the patient, suffering from fever and drenched in perspiration, finds poultices add to his sufferings; in such circumstances they should be avoided. A warm bath given, with due precautions, at the beginning of the disease is often useful. As the anus is apt to become excoriated, it should be washed after each stool with tepid water containing some disinfectant. Ford recommends the application of an ointment containing tannic acid 4 per cent and cocaine 5 per cent. A warmed bed-pan should be used, to prevent the patient getting out of bed.

The *diet* is an all-important point in a disease in which the alimentary canal itself is affected. In most instances the patient should be restricted to a milk diet. Condensed milk will answer if pure fresh milk of good quality cannot be obtained. Milk diet is as valuable in the chronic as in the acute stage, and is specially valuable when there is a scorbutic tendency. The milk may be given pure or diluted with lime-water, and is administered in the intervals between the doses of medicine. For the first few days, unless the patient is in a low state, he should not be urged to take nourishment other than more largely than he desires; and in all cases the needs and feelings of the individual should receive due consideration. When pure milk is not well supported it should be given with full doses of pepsin. Peptonised milk may be substituted. While, in most cases, milk is the best diet for the dysenteric patient, it is not always obtainable, and occasionally it is not well borne in any form by the patient. In exceptional cases barley-water, albumin-water, chicken- or beef-tea may be substituted. When prostration is great and the heart's action feeble, wine, brandy, ammonia, and cardiac tonics are indicated. During convalescence, chicken-broth, arrowroot, and well-boiled rice should be continued for some time, and a return to solid food cautiously made.

In severe cases of tropical dysentery, where not contra-indicated, *ipercacuanha* treatment should be adopted; and I believe that this treatment is also the best for the catarrhal stage of the ordinary epidemic dysentery of temperate climates. It seldom fails when given from the onset of the malady. When the attack has been preceded by constipation, a preliminary dose of sulphate of sodium, castor oil, or calomel to carry off faecal accumulations, and if there are worms a dose

antonin, should be given. If there is no reason to suspect these conditions, 20 to 40 grains of ipecacuanha powder made into a bolus should be given at once, and the dose repeated every six, eight, or twelve hours, according to the urgency of the symptoms and the tolerance of the remedy, until a feculent motion is obtained. If the first dose cause vomiting, this will do good rather than harm, but the second dose should be preceded by a sinapism placed over the pit of the stomach, and 20 to 30 drops of laudanum (for an adult patient) should be given twenty minutes to half an hour before the second dose, and no liquid should be taken for two hours before the bolus is administered. With these precautions, the second dose is seldom rejected. It is better, as a rule, to rely upon the ipecacuanha alone, but when the tormina are very distressing and the calls to stool excessively frequent, from 10 to 15 minims of laudanum may advantageously be added to each bolus. If combined with laudanum, fuller doses of ipecacuanha are to be given. The intervals between the doses should be utilised for the administration of nourishment. Given in this way, the drug causes more or less nausea, but seldom gives rise to troublesome vomiting. Should the ipecacuanha be retained for an hour its therapeutic effect will be secured. There is no use in reducing the dose in order to prevent vomiting. I have seen drachm doses retained where ten grain doses were rejected. The Brazilian method of administration is to pour six ounces of boiling water on a drachm of coarsely powdered ipecacuanha, and at the end of twelve hours to strain off the liquid, which is to be administered to the patient in one draught or in smaller quantities at intervals of two hours. The powder remaining from the first infusion is to be treated again in the same way, and the liquid administered as before, and so for a third time. The process then is to be begun anew with fresh powder in the same or smaller quantity. Various modifications of this plan are in use. This method, which is that practised by Pison, answers well, but is more apt to cause vomiting than the one recommended.

The first sign of improvement is the passage of a feculent stool, which is followed by a decrease of the tormina and tenesmus. The treatment is directed should be maintained for some time after signs of improvement have appeared. When the disease has assumed the characters of a simple diarrhoea, salicylate of bismuth, alone or combined with Dover's powder, will usually prove sufficient to check the looseness, if careful attention be paid to diet.

Decomposed ipecacuanha, first recommended by Surgeon Colonel Harris, has been employed of late years in the treatment of dysentery in doses of 20 to 30 grains. It is not without value, but there is a fairly general consensus of experience to the effect that it is much inferior to the ordinary drug. The nauseating, and even the emetic properties of ipecacuanha, however disagreeable, are, within limits, beneficial in healthy subjects. They have a sedative effect on the circulation, increase the flow of bile, and determine a free action of the skin, with

consequent relief to the portal system, which materially contributes to the cure, especially in acute cases with fever or congestion of the liver. When distressing dysuria does not yield to a warm bath, or when there is extreme pain and restlessness, a hypodermic injection of morphia may be given. When the disease has been confined to the lower bowel and is still at an early stage and attended with severe tenesmus, I have occasionally tried local depletion by means of leeches with apparent advantage, but, besides being a somewhat troublesome remedy, the sites are apt to become inflamed by the discharges.

This treatment by large doses of ipecacuanha has proved so successful that it should not on light grounds be set aside in favour of any other. There is abundant evidence that it succeeds in cases in which other remedies fail. It is contra-indicated in pregnancy, in very debile persons, in phthisical patients, in children of tender age (although they often bear it well), and there are some who cannot tolerate it. In most cases, again, it is unnecessary to subject the patient to the ipecacuanha treatment. When, for any cause, this drug is inadmissible, the *fréquent* treatment, so successfully used in France, should be resorted to. The sulphate of sodium is the salt generally employed, and is given in solution in doses of from  $\frac{1}{4}$  to 1 oz. in the morning. Its purgative action commences from one to four hours after ingestion, and ceases in ten or twelve hours. The dose should then be repeated unless the urgent need for rest require delay. It was remarked by Trousseau that the cure is the more certain the greater the number of the evacuations; still, there is no use in pushing purgation beyond a reasonable limit; and half an ounce of the salt, four times daily, will generally suffice. Trousseau observed, too, that the treatment is much less successful in some epidemics than in others. Major Buchan recommends a drachm of sulphate of sodium in an ounce of fennel water four, six, or eight times a day till every trace of blood and mucus has disappeared. Of 855 cases treated in this way there were only 10 deaths—a mortality of little over 1 per cent. This treatment is advocated by him for acute dysentery only, not for chronic or relapsing cases with ulceration of the colon. It would be a mistake, however, to look for results at all comparable to those obtained in the jail dysentery of India from this treatment in all forms of dysentery. The epidemic dysentery of France, mainly treated by salines, furnishes a case mortality, as we have seen varying from 9 to 14.9 per cent. In the milder forms of the disease the saline treatment leaves nothing to be desired. Experience, so far as it goes, is in favour of attempting to produce asepsis of the intestinal canal by the administration of antiseptic remedies by the mouth, and their use need not interfere with the treatment either by ipecacuanha or salines. Benzo-naphthol is the remedy to be preferred whenever there is suspicion of hepatic or renal complication, and when no such complication exists it is as effective as any intestinal antiseptic at present in use. Thirty to sixty grains may be given during the twenty-four hours in divided doses every two, three, or four hours, in the intervals between



her remedies. Beta-naphthol, resorcin, salol, and naphthalin are used for the same purpose.

Lines act as intestinal evacuants. They deplete the vessels and out, so to speak, the intestinal canal, removing the microbes and that may be present. These indications can also be carried out by use of enemas as adjuvants to other remedies. In mild cases the use of injections is unnecessary. The difficulty formerly experienced in using the patient suffering from the severe forms of rectal dysentery to submit to repeated introductions of the injection-tube is now wholly obviated by the preliminary use of cocaine suppositories, but even with the use of these, injections in a considerable number of cases are neither tolerated nor retained. When the upper part of the bowel is the seat of the disease, enemas, to be of any use, must be large, and the danger of distending a deeply-ulcerated bowel in a condition aptly described by the old Indian practitioners as "rotten" should not be overlooked, although experience has shewn that the risk is much less than is supposed. Experience proves that in severe cases, before extensive disorganisation of the bowel has taken place, large enemas are often of great service. Ford recommends normal salt solution or a 4 per cent solution of sodium bicarbonate for simple lavage of the rectum and sigmoid.

He mentions a case in which the bacillus of dysentery fell from 100 per cent of all organisms present in the stools on the first day to 2·3 per cent on the third day, under the use of enemas of normal salt solution. As an enema in acute dysentery, he uses olive oil alone, or 1½ oz. of olive oil suspended by recent agitation in 2½ pints of milk. The fluid is to be introduced slowly through a long well-oiled rectal tube of large diameter, from a receptacle not more than three feet above the patient's bed. In cases in which hæmorrhages occur the enema should be kept cold, but for routine use it is to be given at a temperature between 100° to 102° F. Boracic acid injections of 1½ pints or more containing a solution of 10 grains to the ounce, repeated two or three times a day were found very useful by Dr. Lillie in South Africa. To relieve pain give 1 to 2 drachms of bismuth with tinct. opii. ℞xxx. in two ounces of starch mucilage may be injected.

In some instances in which the ipecacuanha or saline treatment has failed and the symptoms become more and more aggravated, threatening the development of gangrene, pills containing one grain of calomel, two grains of ipecacuanha, and a quarter of a grain of opium have proved useful. The pills should be repeated every hour at first, until five or six have been given; and then every two hours during the day, and less frequently at night.

The medicine should be continued until an improvement in the patient appears, but should not be carried to salivation. When the stools have changed, ipecacuanha is to be resorted to again in order to complete the cure. When gangrene has actually developed, mercury is contra-indicated.

When dysentery is complicated with malaria, quinine must be given orally or hypodermically in addition to ipecacuanha or salines. In

a form of dysentery affecting the cæcum and ascending colon associated with a malignant type of malaria, accompanied by great prostration and a tendency to collapse, in which the use of ipecacuanha or salines was contra-indicated moderate purgative doses of oil of turpentine and castor oil seemed to me of service. I have also resorted to turpentine with castor oil in smaller, repeated doses, as a stimulant and antiseptic in the treatment of gangrenous dysentery when ipecacuanha had failed, and with apparent benefit in some instances. Ford considers oil of turpentine "highly serviceable in all cases of bacillary dysentery, especially in those where there is pronounced tympanites and great prostration." He gives it in doses of from one fourth to one half gramme every two hours. Turpentine should be avoided if there is kidney disease. Should algidus manifest itself, warm applications to the extremities, stimulants internally in small and repeated doses, and subcutaneous injections of ether are indicated.

In the hæmorrhagic form associated with malaria, which has seldom any relation to true dysentery, quinine and the tincture of the perchloride of iron should be given. Mateo infusion by mouth and rectum was found serviceable in the malignant hæmorrhagic dysentery occurring in Trinidad, already mentioned under the name "Bisheco," or epistemic gangrenous proctitis, and injections of lime juice have also been employed with advantage. The value of ergotin in hypodermic injection should not be overlooked if there be reason to suppose that an eroded vessel is the source of the hæmorrhage. Adrenalin has been recommended, but in Ceylon the results were disappointing. Applications of ice to the abdomen and injections of feed water may also be tried in hæmorrhagic cases. In the scorbutic form, in addition to the regulation of the diet which should include the use of lemons, limes, oranges, or grapes fresh fruit has been strongly recommended. Maclean found it most useful when given in the form of a sherbet. When the motions in scorbutic dysentery contain much dark and liquid blood, 15 to 30 minims of oil of turpentine in almond emulsion will often act like a charm. When turpentine is contra-indicated, a solution of one of the astringent salts of iron may be used. There is a dysenteric scorbutus as well as a scorbutic dysentery, the drain on the system causing scorbutic spots. In this form the primary indication is to stop the drain. Arthritis appearing in the course of dysentery demands only the use of local applications. When symptoms of hepatic congestion appear in the early stages of tropical dysentery, as they frequently do, our aim ought to be to clear the large intestine of infective organisms by a purgative or by mild antiseptic irrigations of the bowel, but this complication should not be allowed to interfere with the administration of ipecacuanha which acts favourably on liver and bowels alike. Among the numerous remedies employed in acute dysentery, it will suffice to mention cinnamon in drachm doses, three or four times daily. Sulphur, half a drachm to a drachm three times daily, alone or with 5 grains of Dover's powder. Tincture of *Moussonia ovata* (2½ oz. of the dried plant to a pint of rectified

spirit) in doses up to half an ounce in water; creosote in doses of two drops in mucilage every two hours.

In the dysenteric diarrhoea of children, the question of feeding is of primary importance. There is no advantage in putting either a breast- or bottle-fed infant on other food if there be no vomiting and the milk be well digested. In the case of bottle-fed children, the purity of the milk and its dilution in relation to the age of the patient has to be considered. When milk disagrees, barley-water, water from toasted oatmeal, chicken- or beef-tea, albumin-water, or some other suitable substitute must be selected and its effects watched. In the more protracted cases, lean raw meat, very finely minced, may be given in one or two teaspoonful doses at a time, and four times daily or oftener.

A dose of castor oil should be given at once to clear out the bowels, and repeated in smaller doses, in the form of emulsion, once or twice a day to keep them freely open. In a few days the character of the motions will change, and salicylate of bismuth, 1 to 3 grains every four hours, will restrain the remaining looseness. In some cases alterative doses of calomel or grey powder are of service. When these measures fail, teaspoonful doses of a solution of perchloride of mercury ( $\frac{1}{140}$  to  $\frac{1}{120}$  grain), first hourly, then at longer intervals, will often effect a rapid improvement. When the lower bowel is chiefly affected, it may be washed out from time to time with some mild antiseptic injection.

A. D.

*Vaccination and Serum-therapy.*—Shiga produced antidysenteric serum in the horse by inoculating cultures of the dysentery bacillus. This serum was used successfully in the treatment of the endemic dysentery of Japan. It should be administered early in the attack, as its beneficial effects are less evident at later periods. The mortality of the Japanese disease during the epidemic of 1898-99 was from 28.5 to 37.9 per cent in cases treated in the ordinary way, and from 8 per cent to 12 per cent in cases treated with the serum. I have employed an antidysenteric serum from the horse in the treatment of adults and of children, the latter suffering from the diarrhoeal diseases of the warm summer months. The adult cases appeared to be benefited, since the attack was brought to an abrupt termination; but the number of cases treated was small and the epidemic relatively mild in type. In the children no definitely beneficial result was obtained. In the latter the serum was, however, often employed late in the course of the disease. Kruse has also reported favourably upon the use of an antidysenteric serum. Our present knowledge justifies the employment of the serum in acute bacillary dysentery, and if the injections be made within the first two or three days of the disease, beneficial effects may be expected. The use of the serum later, after severe lesions of the intestinal wall have been produced, is, apparently, of far less value. A final opinion on the value of the serum treatment of dysentery bacilli diarrhoeas of children cannot be given at this time.

Vaccination of small animals with attenuated and dead cultures of

dysentery bacillus is followed by an active immunity, which in the guinea-pig persists for many weeks. No doubt a similar method of vaccination is applicable to man. The use, however, of dead cultures alone is not advisable, because of the painful local reaction set up. The bacilli should either be modified in action by admixture with an antydysenteric serum, or, possibly, autolysed products of the bacilli alone be employed since by means of the latter a certain degree of immunity can be produced in experimental animals. Protective vaccination in man with the dysentery bacillus has not yet been placed upon a definite experimental foundation.

S. F.

*Treatment of Chronic Dysentery.*—Chronic dysentery occurring in European residents in tropical countries demands a change to a temperate climate. Minute directions as to the precautions necessary to avoid or mitigate the possible dangers of such a change should be given. If the voyage has to be undertaken in winter, a short stay on the Riviera may be advisable. The patient should wear a flannel belt sufficiently wide to cover the whole abdominal region. The sea voyage itself is often beneficial when the arrangements on board for invalids are good. But a short voyage may sometimes be recommended with advantage in the case of those who cannot afford the time and expense involved by a prolonged stay in Europe. Warm clothing, avoidance of draughts, careful regulation of diet, and change to a temperate climate should be looked upon as the most important measures in the treatment of this disease.

During exacerbations, the diet must be restricted to milk, the patient kept in bed, and the treatment adapted to the acute disease employed, modified, however, according to the urgency of the symptoms. During these exacerbations I have used an infusion of 100 grains each of ipecacuanha and sumbulu, and 200 of cinnamon in 10 ounces of water, giving half an ounce to 1 ounce of this every four or six hours. The disease is a protracted one, and this has to be taken into account in regulating treatment, diet, and exercise, and as the patient is weak, nourishing, easily digested food is essential. When walking is inadvisable or impossible, carriage exercise is to be taken as frequently as the weather and state of the patient permit.

The whole course of the large intestine should be carefully explored in order to detect swelling, hardness, or tenderness. From a careful consideration of the results so obtained, and of the character of the stools, an effort should be made to arrive at an estimate of the existence and sites of cicatrices, ulcers, and congestion. When the existence of ulceration is inferred, constipation must be obviated by the gentlest laxatives, and diarrhoea checked by the guarded use of the mildest astringents, accompanied, if gastric or intestinal fermentations be suspected, by antiseptics. When cicatricial contractions in the lower part of the bowel interfere with its evacuation, emollient and antiseptic enemata may give relief. In chronic ulceration, especially when seated in the lower part of the bowel, enemata of nitrate of silver have frequently

ineficial. Sir P. Manson recommends them of a strength of from grain to 1 grain per oz. of distilled water, when acute symptoms appeared. Two or three pints of this solution are to be injected when the bowel has been well cleaned out by castor oil and a large enemata, the patient being encouraged to retain the injection as long as possible. The injections may be repeated every few days, if they appear to do good—not otherwise. Dr. Sandwith prefers sulphate of iron to  $1\frac{1}{2}$  grains to the ounce, from his experience in Egypt, where, the disease is chiefly of the amœbic variety. A wet compress on the abdomen is not only grateful to the patient, but often has a beneficial influence on the congested bowel.

Hot baths, gentle laxatives, massage to the abdomen, and emollient, and antiseptic enemas must be our chief resort in those hopeless cases in which partial stenosis is established. It is remarkable how many of these hopeless cases do improve, how some even recover fair health; this should encourage us not to despair, the distressing helplessness of the physician in presence of the aggravated forms of chronic dysentery should lead us, by greater attention in the treatment of the disease, to render the chronic form of less and less frequent occurrence.

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A. D.

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S. F.

## II.—AMŒBIC DYSENTERY

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Section on Amœba by SIMON FLEXNER, M.D.

**Geographical and Topographical Incidence.**—We have reports of many cases of amœbic dysentery of indigenous origin from St. Petersburg, Königsberg, Kiel, Hamburg, Berlin, and other towns in the north of Europe. The disease has not been recognised in, but is, perhaps, not absent from England. It is of more frequent occurrence in the east and southern regions of Europe, without, however, attaining endemic proportions. On the Western Continent isolated cases have been seen by Henshaw in Michigan and by Musser in Philadelphia, and they become more numerous in the middle and southern States. Prof. Osler says that "acute dysentery is the commonest variety throughout the United States, and cases of acute and chronic dysentery admitted into his wards (Copenhagen) having been almost exclusively of this form. From the comparative rarity of liver abscess in some of the West

India Islands, it may be inferred that amœbic dysentery is not of frequent occurrence. Dr. D. M. Ross says, "I have never seen a case of hepatic abscess follow dysentery contracted in Jamaica." This agrees with earlier accounts. In Cuba, Martinique, and some of the other islands, amœbic dysentery is more common. In British, Dutch, and French Guiana it is not very common, but is the prevailing form of dysentery in Rio de Janeiro and many other parts of Brazil, and in the north of Chile.

Egypt may be said to be the home of this disease, since, from all accounts, it is the form of dysentery almost exclusively observed there. It is not so certain, however, to what extent it prevails as a pure infection. In Algeria and Senegal, although less common than in Egypt, it is frequent. No part of tropical Africa with which we are acquainted is free from amœbic dysentery, but in the ordinary circumstances of life, that is, apart from military expeditions, it does not appear to be so common on many parts of the West Coast as the bacillary kind. In the island of Mauritius it is endemic. In South Africa amœbic dysentery is, upon the whole, rare. Major Beveridge found amœbæ in three cases only of dysentery which he examined. It is also rare in Ceylon, where Castellani found amœbæ twice in 150 examinations of dysenteric stools. In the Upper Provinces of India, according to Duncan, the disease is seldom met with, and in Calcutta, where it is more prevalent, the bacillary is still the common form. Amœbic dysentery exists in Siam, Indo-China, and many parts of China proper, but to what extent is uncertain. It is very prevalent in the Philippine Islands, where it has been the scourge of the American troops. Strong and Musgrave noted 766 cases of bacillary dysentery to 561 of the amœbic form.

Little definite is known respecting the character of the localities where amœbic dysentery prevails, but it is well ascertained that local conditions are of considerable significance for its endemicity. Laker states that in North America the disease has been observed more frequently in districts approaching the sea-level, the shores of the Chesapeake Bay, the Gulf of Mexico, and the Mississippi Valley. In India, too, it appears to be more common on the coast-line than in the interior, but, according to Fernando, the contrary is the case in Ceylon, where the hill districts suffer most. The remarkable prevalence of the disease in Egypt is probably connected with the annual inundations of the Nile, and their effects on soil and water-supply. It may be safely asserted that its prevalence will always be found to be largely determined by sanitation and water-supply.

**Sources and Vehicles of Infection.**—Soil and water are the natural and common habitats of amœbæ. In warm climates they abound not only in surface waters, but in cisterns, tanks, and in the pipe-water of eastern cities. These organisms are, in fact, so constantly and abundantly present in drinking water in tropical and subtropical countries that if all or most, of the amœbæ present in water were pathogenetic, amœbic dysentery should be everywhere one of the commonest of diseases. The common vehicle of infection is believed to be drinking water. The

ence of this is inferential. Instances have been recorded in which it has been found that patients suffering from amœbic dysentery have drunk their water from cisterns swarming with amœbæ. Musgrave ascribed the disease to spread almost epidemically in Manila after a flood, which resulted in the washing out of cesspools and other places. However, but for this flooding, the parasites might have remained harmless. The almost entire absence of amœbic dysentery from the Indian prisons is another reason for believing that drinking water is an important vehicle of infection. Uncooked vegetables and fruits are, perhaps, almost the frequent vehicles of the infection in tropical countries as water. In some parts of the East the dangerous practice prevails of watering garden vegetables with diluted human fæces, which, as Schaudinn has shewn, may retain powers of infection for at least four weeks. Musgrave and Clegg isolated an amœba, pathogenetic to animals, from a lettuce that had already been washed several times with more care than the ordinary house-maid bestows on the cleansing of vegetables. Sodré believes that infection is often conveyed by the air; and the great resistance to drought exhibited by encysted amœbæ leaves little doubt that amœbæ may be frequently carried into water and food by air currents. Fingers and utensils soiled with substances containing encysted parasites must also be reckoned among the vehicles of infection. Dopter reports an instance in which soldiers who had never been out of France contracted amœbic dysentery after living in a room occupied shortly before by patients with the disease. This shews the danger of propagation of the disease in temperate climates by chronic cases.

**Seasonal Prevalence.**—Major Rogers failed to find any marked seasonal differences in the admissions for amœbic dysentery in Calcutta. Jourdain, on the other hand, states that out of 13 cases observed at Timore, 12 occurred during the warm season. It may be inferred from these facts that when the temperature of the year is fairly uniform the disease may be equally distributed over the different seasons, but when there is a well-marked winter and summer season the bulk of the cases will fall in the latter.

There is some evidence that the prevalence of amœbic dysentery in a country varies considerably in different years. Craig observed that, whereas the cases from the Philippines admitted into the Army Hospital at San Francisco in 1899-1900 were mostly bacillary, those received afterwards were chiefly amœbic. Morgenroth, in the same way, found amœbæ entirely absent from the stools of dysenteric patients in China in certain seasons and years, while at other times they were invariably present. The cause of these irregular fluctuations is unknown.

**Personal Factors**—*Age.*—Children have the disease in a milder form than adults, but the relative liability of the different age-periods has not been determined. *Race.*—It is doubtful whether race has any influence on susceptibility, but habituation counts for much. The natives of a locality where amœbic dysentery is endemic are less subject to the infection than strangers, and in them the disease is more amenable to

treatment. The unacclimatised Caucasian is especially susceptible. This cannot be ascribed to the less favourable sanitary conditions under which he lives, as compared with the native, nor to the less care taken to secure pure drinking water. His liability is rather the effect of climate, giving rise to intestinal congestions, accentuated by alcoholic indulgence and the use of a diet unsuited to his new conditions of life. Sex by itself has no influence on susceptibility. The smaller proportion of women attacked is due to their more temperate habits, and to less exposure to the exciting causes of the disease. It has been observed in the Philippines that troops engaged on active service, and consequently exposed to fatigue and vicissitudes of weather, furnish a larger proportion of cases than those living in quarters.

A. D.

**Amoeba.**—*Amoeba of the Intestinal Canal in Man.*—Lambl in 1860 was the first to call attention to amoebæ in the stools. The bodies described by him as amoebæ occurred in a child, and varied in size from  $4.6 \mu$  to  $6.2 \mu$ , but there is some doubt whether they were really amoebæ. Ten years later Lewis observed amoebæ in the dejections of 1 per cent of cholera patients examined by him in India, but did not attach any pathological significance to them. Of far greater interest is the observation of Loesch, made at about this time, but published three years later. In the stools of a man aged twenty-four years, who suffered from chronic diarrhoea, Loesch found numerous motile amoebæ, which were from five to eight times the size of red corpuscles. The amoebæ are accurately described, and agree in all essential features with the pathogenetic amoeba of the human intestine as now accepted. At the first examination the amoebæ were so numerous that there were as many as sixty to seventy in one field of the microscope. Ordinary treatment was not followed by a  $\gamma$  improvement; but after Loesch found that a solution of quinine 1:5000 quickly killed the amoebæ, and injected this solution into the bowel and administered the drug by the mouth; the patient improved, and the amoebæ disappeared from the stools, only to reappear, however, when the quinine injections were left off. Pleurisy developed, and later the amoebæ, without special treatment, disappeared from the stools, and were not found again up to the time of death, which was caused by pneumonia. The autopsy showed chronic ulceration of the large intestine. Portions of the stools containing amoebæ were injected into four dogs. Three of the dogs remained well, the fourth developed, eight days later, mucous stools containing the amoebæ. The animal was killed, and an examination of the large intestine showed congestion and ulceration. Loesch, however, did not regard the amoebæ as the direct cause of the lesions, but merely as an additional irritant in the course of an ordinary dysentery. Loesch's publication was followed by that of Grassi, who held that amoebæ occurred in the dejecta of healthy persons and of those suffering from diarrhoea, and that although they were more numerous in the latter condition they had no special pathological significance. Grassi observed that the amoebæ sometimes included leucocytes, red corpuscles, and starch, which

he regarded as food. Cunningham and Lewis, who found amœbæ in healthy persons and in patients suffering from cholera and other diseases, erroneously considered them as transitional stages of flagellates and sporozoa. Robert Koch was the first to pay attention, in Egypt, to the amœbæ of the intestine. In 1883, in the course of his work on cholera, he found in the ulcerated intestine of four cases of dysentery amœbæ which were readily differentiated with aniline dyes. In one case only, in which the ulcers were healed, were they missed. He failed to find them in the mucus; but he regarded their presence in the deeper parts of the ulcers as indicating a causal relationship to dysentery. Stimulated by these observations and Koch's advice, Kartulis investigated numerous cases of dysentery in which amœbæ occurred, and he noted a relation between the numbers of the organisms and the severity of the symptoms. The interest aroused by Kartulis's publications brought to light several observations by Normand, Sonsino, and Perroncito, which followed Loesch's paper, and dealt with amœbæ in colitis. A series of confirmatory observations appeared. Hlava reported the positive examination of sixty cases of dysentery, and the injections of laboratory animals with faeces containing amœbæ. Of six cats and seventeen dogs which he inoculated he obtained in four cats and two dogs results which he regarded to be positive, but did not describe. In the United States Drs. Osler, Councilman and Lafleur, Simon, Musser, Stengel, and others observed amœbæ in cases of dysentery, and regarded them as identical with those described by Loesch and by Kartulis. At about the same time Fenoglio of Sorrento described amœbæ, associated with cercomonads and the eggs of *Trichocephalus trichiurus*, in a case of diarrhoea, but denied that the amœbæ had any pathogenetic properties, while Calandruccio swallowed encysted amœbæ, which developed and were still present twelve days later in his normal stools. Massiutin also reported from Loesch's clinic in Kiew that amœbæ were found in intestinal diseases other than dysentery. Further results confirmatory of Kartulis's were soon supplied from Germany by Cahen, Nasse, and Quinke and Roos, from Austria by Kovacs, from Brazil by Lutz, so that at present there is a large number of papers supporting this opinion. Kartulis in his later papers has greatly increased the number of cases of dysentery examined with positive results, and the cases of other intestinal diseases showing negative results. He also asserts that he has cultivated the dysentery amœbæ in a hay infusion, but this is probably a mistake. He undoubtedly succeeded, however, in inducing in a cat, by the injection of fresh dysenteric faeces, an attack of dysentery. The stools contained amœbæ, and the cat died on the twelfth day. Kartulis states that he has produced similar lesions with the cultivated amœbæ, and with the pus from a liver abscess containing amœbæ but no bacteria.

That special forms of dysentery and of hepatic abscess due to amœbæ exist is established by these observations. More recent work has been centred round the identity and mode of pathogenetic action of the amœbæ described by various authors, and on the amœbæ occurring in the



intestines of patients suffering from diseases other than dysentery, and of healthy persons. The descriptions of amoebae as given by Grassi do not agree precisely with those given by Loesch, and in his earlier paper Kartulis did not give consistent descriptions. Moreover, it is doubtful whether the organisms ingested by Calandruccio are to be regarded as identical with the amoebae of Loesch and of Kartulis.

One of the earliest attempts at separation of a virulent from a mild form of amoebae was made by Quinke and Roos. They observed two cases of amoebic colitis, in the first of which the infection was caused by an organism agreeing with the amoeba of Loesch (*Amoeba coli*), while in the second the stools contained, besides flagellates, a considerable number of amoebae larger in size than the former variety, and shewing a different encysted state from that of the *Amoeba coli*. The symptoms in the second patient were less severe than in the first. With the stools of the first patient eight cats were injected per anum; six developed dysentery and died in two to three weeks, shewing ulceration of the large intestine at the autopsies. Two cats were fed with non-encysted amoebae and were unaffected, four others were fed on the encysted form and developed dysentery. The stools of the second patient produced no morbid changes in cats. On account of these differences Quinke and Roos proposed to call the second organism *Amoeba coli mildis*. Quinke and Roos also investigated the normal intestine as regards the presence of amoebae. They administered Carlsbad salts to twenty-four persons, in nine of whom amoebae were found. These amoeba-containing stools are almost without action on cats. This third, harmless variety they call *Amoeba cucurbita*. Schuberg also succeeded in obtaining amoebae from the stools of healthy persons by administering Carlsbad salts. He considers them to be normally present in the small intestine in man. A similar but more extensive investigation was carried out by Kruse and Pasquale. While in Italy, en route to Egypt, they noted the appearance of amoebae in their stools which remained normal, and in Egypt they twice found amoebae in the stools from thirty five healthy persons. Hence they conclude that in some countries amoebae are occasionally normal inhabitants of the intestine. Their work on amoebic dysentery confirmed that of Kartulis and of Councilman and Laffeur. They failed to cultivate the amoeba from dysenteric stools, but with faeces, and with the pus from abscesses of the liver, they succeeded in producing dysentery in cats. In three of the successful experiments with the pus of hepatic abscesses bacteria were absent. They recognised a pathogenetic *Amoeba dysenteriae* as apart from the non-pathogenetic *Amoeba coli*, a distinction introduced by Councilman and Laffeur. The experiment of Zancarol is interesting as bearing upon the power of pus from an hepatic abscess, in which amoebae could not be found, to set up dysentery in cats. Hence he concluded that sterility is not to be decided upon the grounds of bacteriological examination alone.

As is shewn by Boas's results and the partial failures of other experimenters, dysentery is not invariably set up in cats by the injection of faeces containing amoebae. Since the evidence is strong that the bacterial



and chemical constituents of faeces do not produce dysentery in cats, and since in the successful experiments amœbæ were always present in the injected material, it may be concluded that these organisms are the essential factors, although, owing either to some peculiarity of condition or stage of development in the parasites, to their numbers, or to the greater resistance in certain cats, and possibly, also, to the mode of injection, some only of the inoculated animals develop the symptoms and lesions of amœbic dysentery. Harris, who succeeded in producing dysentery in puppies by the injection into the rectum of stools containing amœbæ, with the production in one instance of an amœbic abscess of the liver, failed entirely to produce a similar lesion by the inoculation of cultures of all the bacteria that could be isolated from the stools. Kruse and Pasquale also failed to set up dysentery in cats by means of bacterial cultures of dysenteric stools or with amœbæ-free stools of dysenteric patients. Marchoux was successful in causing dysentery by means of amœbic stools in a series of twenty cats, and in those which survived the injections for fifteen days or longer, abscesses of the liver, single, as a rule, but sometimes multiple, developed. Once seven or eight small abscesses were encountered. Heating the dejecta to 45° C. for thirty-five minutes, which destroys the amœbæ but not the bacteria, rendered the injections negative.

The evidence which these observations supply is to the effect that in the intestine of man amœbæ are not uncommonly present as saprophytes, and in the tropics and many countries of subtropical and temperate climates a species of pathogenetic amœba also exists which is capable of producing dysentery and hepatic abscess. The peculiar form of dysentery caused by this parasitic amœba, to distinguish it from the dysenteric disease caused by the *Bacillus dysenteriae*, is called amœbic dysentery; and the hepatic abscess produced by the invasion of amœbæ into the liver is called amœbic abscess. It is possible to produce experimentally in cats and young dogs a fatal form of colitis, in which the symptoms and lesions are those of dysentery in man, and in some instances the lesions in the colon have been followed by the appearance of hepatic abscesses resembling those in man.

*Biology of the Amœba of the Intestinal Canal in Man* The importance of obtaining cultures of the amœbic outside the body has been clear to all investigators of this subject. The results, up to the very recent publication of Musgrave and Clegg, have been negative so far as the pathogenetic species in man is concerned. Cunningham, Grassi, Kartulis, and Vivaldi believed that they had cultivated the *Amœba coli*. In spite of the more or less successful inoculations of cats with these cultures by Kartulis and Vivaldi, it is extremely doubtful whether they really worked with cultures of this amœba. Kruse and Pasquale failed to cultivate *Amœba coli*, although they obtained cultures of saprophytic amœbæ by following the methods of the previous investigators. Saprophytic amœbæ have been grown on solid culture media, on which they have been separated more or less completely from extraneous substances except

India Islands, it may be inferred that amœbic dysentery is not of frequent occurrence. Dr U. M. Ross says, "I have never seen a case of hepatic abscess follow dysentery contracted in Jamaica." This agrees with earlier accounts. In Cuba, Martinique, and some of the other islands, amœbic dysentery is more common. In British, Dutch, and French Guiana it is not very common, but is the prevailing form of dysentery in Rio de Janeiro and many other parts of Brazil, and in the north of Chile.

Egypt may be said to be the home of this disease, since, from all accounts, it is the form of dysentery almost exclusively observed there. It is not so certain, however, to what extent it prevails as a pure infection. In Algeria and Senegal, although less common than in Egypt, it is frequent. No part of tropical Africa with which we are acquainted is free from amœbic dysentery, but in the ordinary circumstances of life, that is, apart from military expeditions, it does not appear to be so common on many parts of the West Coast as the bacillary kind. In the island of Mauritius it is endemic. In South Africa amœbic dysentery is, upon the whole, rare. Major Beveridge found amœbæ in three cases only of dysentery which he examined. It is also rare in Ceylon, where Castellani found amœbæ twice in 150 examinations of dysenteric stools. In the Upper Provinces of India, according to Duncan, the disease is seldom met with, and in Calcutta, where it is more prevalent, the bacillary is still the common form. Amœbic dysentery exists in Siam, Indo-China, and many parts of China proper, but to what extent is uncertain. It is very prevalent in the Philippine Islands, where it has been the scourge of the American troops. Strong and Musgrave noted 766 cases of bacillary dysentery to 561 of the amœbic form.

Little definite is known respecting the character of the localities where amœbic dysentery prevails, but it is well ascertained that local conditions are of considerable significance for its endemicity. Latham states that in North America the disease has been observed more frequently in districts approaching the sea level, the shores of the Chesapeake Bay, the Gulf of Mexico, and the Mississippi Valley. In India, too, it appears to be more common on the coast line than in the interior, but, according to Fernando, the contrary is the case in Ceylon, where the hill districts suffer most. The remarkable prevalence of the disease in Egypt is probably connected with the annual inundations of the Nile, and their effects on soil and water supply. It may be safely asserted that its prevalence will always be found to be largely determined by sanitation and water supply.

**Sources and Vehicles of Infection.** Soil and water are the natural and common habitats of amœbæ. In warm climates they abound not only in surface waters, but in cisterns, tanks, and in the pipe water of eastern cities. These organisms are, in fact, so constantly and abundantly present in drinking water in tropical and subtropical countries that if all, or most, of the amœbæ present in water were pathogenetic, amœbic dysentery should be everywhere one of the commonest of diseases. The common vehicle of infection is believed to be drinking water. The

studied successfully by Casagrandi and Barbagallo, and especially by Schaudinn. The first authors have given an exact account of the development of the non-pathogenetic species, while Schaudinn has continued and extended their studies, and brought to light many facts of the development of the pathogenetic species. According to the nomenclature introduced by Schaudinn the first should be called *Entamoeba coli*; and the second, *Entamoeba histolytica*. (For the morphology of the Amœba, see p. 17.)

Schaudinn would seem to have succeeded in causing dysentery in cats by means of spores of *Amœba histolytica*. A small portion of fæces was dried in the air, and then suspended in a small quantity of water; from the thick suspension microscopical preparations were prepared, and on careful examination were found to be free from encysted forms, but to contain spores of the amœba. The material was now washed off the slides with water mixed with milk, and administered by the mouth to cats; two of these developed dysentery—a young animal, which died of the disease and shewed early and characteristic lesions, and an older one which eventually recovered. The stools of the animals, free from amœbæ before the experiment, contained many after the administration of the emulsion. That the lesions of amœbic dysentery can be produced by the ingestion of spores of *Amœba histolytica* is rendered highly probable by this result.

SIMON FLEXNER.

**Morbid Anatomy—Site of Lesion.**—The whole of the large intestine may be involved, but the lesions seldom extend above the ileo-cæcal valve. Frequently they are limited to one segment of the intestine, or, at least, the brunt of the disease falls on one part, the rest of the bowel being only slightly affected. Kartulis found the whole of the large intestine involved in half the cases observed in Egypt; in one-fourth the site of the disease was the descending colon and sigmoid flexure; in the other fourth the cæcum was affected together with the ascending or the descending colon, or the rectum. The rectum was affected in one-fifth of his cases, and the cæcum alone in only one-twentieth. Major Rogers, Calcutta, found the lesions most marked in the cæcum and ascending colon, and not rarely limited to these parts. Lafleur likewise states that in the majority of cases the cæcum and ascending colon are affected. This agrees with my own observations. In seven out of one hundred and twenty necropsies by Musgrave in the Philippine Islands, amœbic infection of the appendix was found, and in three of these the cæcum was also inflamed, and death resulted from peritonitis following perforation. The evidence points to a varying localisation of the lesions in different countries, for which no explanation can be offered. Does it depend on the varying frequency of mixed infections in different countries?

The characteristic lesion of amœbic dysentery consists in circumscribed areas of thickening and necrosis in the submucosa, which appear as sharply defined nodules projecting into the lumen of the bowel, giving

rise to ulcers with thickened, undermined edges—the mucosa itself being involved secondarily and to a less extent. The nodules vary in size from that of a hemp-seed to a pea or bean. The smaller ones are round, the larger oval, and are most frequently seated on the folds of the mucous membrane. On incision they are found to contain a grayish-yellow viscid substance, consisting of broken-down tissue, red blood-corpuscles, a few pus-cells, and amœbæ. The necrosis of the mucosa gives rise to a small opening, communicating with the focus of disease in the submucosa. An ulcer is thus established which increases by extension of the necrotic process in the submucous tissue, and, to a less extent, by the destruction of the overlying mucous membrane, giving rise to the characteristic ulcer *en bouton de chemise*. The ulcers thus formed are round or oval, and in the latter case are seated transversely to the long axis of the bowel. They vary in size from a few lines to one or two inches, and, by coalescence with neighbouring ulcers, they are often much larger and irregular in form. They vary greatly in depth. As a rule, their base is the submucosa; sometimes it is formed by the muscular coat, and in severe cases their floor is formed by the thickened subserous tissue. The ulcer, when recent, is covered by a tawny, gelatinous coating, consisting of necrosed tissue, amœbæ, red blood-corpuscles, a few pus-cells, and bacteria: the last are most abundant in the superficial layer. The base is covered with a dark slough when gangrene is present. In chronic ulcers the base is thickened, pale, and sometimes pigmented. When the healing process sets in the ulcer presents a clean, granulating surface. The borders of the characteristic amœbic ulcer are raised above the level of the surrounding healthy mucosa. In recent cases the edges are ragged and undermined, fistulous tracks often connecting neighbouring ulcers. For a varying distance from the margin of the ulcer the submucosa is thickened, œdematous, softened, infiltrated with lymphocytes, and contains amœbæ, especially along the advancing line of necrosis. The cells of the tissue undergo degeneration, and the intercellular substance breaks down into a necrotic mass. The lymphatics are dilated, the blood-vessels congested or thrombosed, and their walls infiltrated with round cells. The mucosa is comparatively slightly affected. The tubular glands in the immediate neighbourhood of the ulcers will be found more or less dilated, distorted, or cystic; their epithelium cloudy, swollen, or detached. The solitary follicles are sometimes enlarged or ulcerated, at other times normal. The mucosa between the ulcers is generally normal, but patches of superficial necrosis, of bacillary origin, are occasionally observed. When massive gangrene occurs, larger or smaller sloughs, or even tubular portions of the inner coats, may be passed by stool, leaving ulcers which present no specific characters.

The amœbæ are found in the viscid contents of the nodules, in the gelatinous matter covering the ulcers, and in the extending area of necrosis in the submucosa. When the muscular coat is involved, they are found, according to Lafleur, “exclusively in the intermuscular septa of connective tissue, in the loose meshes of the subserous connective

and may even invade the fat of the mesocolon." Amœbæ are also met with in the lymphatics and veins.

What path do the amœbæ reach the submucous tissue? Many hold that they penetrate by the interglandular tissue. Jürgens and Schaudinn hold that they enter by Lieberkühn's crypts, and Schaudinn is at the same conclusion. "I frequently find amœbæ," he says, "in as yet, healthy parts of the mucosa in the glands of Lieberkühn, and then follow them into the submucosa." It is by no means certain, however, that they always follow the same route.

In the more chronic cases the bowel contains ulcers in all stages of evolution and repair. The mucous surface of the intestine is here pale, here congested, in another part pigmented. Pigmented spots, indicating sites of small ulcers, are seen along with linear or radiating cicatrices, a result of more extensive lesions. Side by side there may be chronic ulcers with callous, thickened edges, but still containing amœbæ, recent ulcers with ragged edges, and sloughing lesions of varying extent. In short, the pathological *facies* of chronic amœbic dysentery differs in different cases and in different parts of the same bowel. In the more severe cases long standing, the wall of the bowel is thickened and hard, and its lumen contracted. Sometimes distinct cicatricial contractions are present, over which the bowel is dilated. The peritoneum participates in the process. It is thickened and discoloured at parts corresponding to deep ulcers. Adhesions often exist between the large intestine and the coils of the small intestine, the wall of the abdomen, or the neighbouring organs, giving rise to displacements. Perforation, followed by general peritonitis, is by no means a rare termination of this dangerous malady. A circumscript abscess is also met with.

**Symptoms—Acute Form.**—The onset of amœbic dysentery is occasionally sudden and its course acute. So far as my experience goes, the acute form is rare in the tropics, but it is possible that cases of this kind have been mistaken for bacillary dysentery. The patient is seized with colicky pains and tenesmus, often severe in proportion to the gravity of the disease. The stools are at first frequent and scanty, consisting of mucus alone or mucus streaked with blood, or mixed with thin faecal matters. After a few days they become more copious, watery, and eddy, of a brownish-red colour, or they present the consistence of jelly, semi-viscid from admixture of mucus, with a yellow, green, or streaked scum and a little fluid blood floating on the surface. If gangrene sets in, sloughs of varying size and thickness, with clots of blood, are passed—the motions acquiring at the same time an insufferably offensive, gangrenous odour. At this stage the motions may become less frequent and the tenesmus less severe, giving rise to delusive hopes of amendment. A considerable amount of pure blood—fluid or clotted—is sometimes passed. Much more rarely dangerous hæmorrhage occurs. The temperature for the first few days ranges from 99° to 102°, seldom rising 103° F.; towards the end it falls below normal. The pulse is moderately accelerated at the commencement, becoming rapid and weak



as the disease advances. The appetite is lost. The tongue, at first moist, becomes dry and brown as a fatal issue is approaching. Marked prostration is always present in dangerous cases. The urine often contains a trace of albumin. Death takes place in a week or ten days from exhaustion or from perforation with general peritonitis. In the less severe forms recovery—permanent or temporary—occurs, or the symptoms gradually moderate, persisting in a milder form to prove fatal or end in recovery at a later period. Acute or subacute attacks, instead of opening the scene, may occur during the course of the chronic disease.

*Chronic Form.* Amœbic dysentery in the vast majority of cases runs a chronic course, with irregularly recurring periods of quiescence and exacerbations. It often begins quite insidiously. A case is reported in which amœbic dysentery, followed by liver abscess, occurred in England, two years after the patient had returned from the Mediterranean. It had apparently been latent all this time. In some, even of the cases of acute onset, ulcers have been found in the bowel which must have dated back for months before the acute attack began, and had been attended with such mild symptoms as not to attract the notice of the patient. At times the bowels are somewhat loose, but this hardly attracts attention, and there are intervals, more or less prolonged, during which the bowels are regular or constipated. This state of things may last for several months—occasionally even for one or two years—with little disturbance of the general health. The patient feels, indeed, that he has lost something of his usual vigour, but is able to attend to his duties, until, perhaps, a more severe exacerbation, attended with colic, tenesmus, and abdominal pain, makes him seek advice. The disease may run on in this insidious way, without its real nature being suspected, until liver abscess or perforation supervenes. An officer, supposed to be suffering from indigestion and “liver,” with loss of appetite and irregularity of the bowels, continued to perform his ordinary, and by no means light, duties in the Royal Engineers, until within a few days of his death from perforation, which was the first thing to open the eyes of his medical attendants to the nature of the disease.

The exacerbations in mild cases last from two to five days. The stools are loose and alkaline, containing mucus and perhaps a little blood from time to time. The motions seldom exceed six in the twenty-four hours, and are passed with little pain. By rest, dieting, or treatment the symptoms subside for a time,—the stools becoming more or less formed. In not a few cases there is constipation. The formed or pulpy stools will frequently be found to be streaked or mixed with mucus containing amœbæ. This period of quiescence lasts from ten to fourteen days, more or less, to be followed by another exacerbation.

In the graver forms developing out of the milder types, or in those which have been severe from the commencement, the intermissions are shorter, the exacerbations more prolonged, and the stools during the latter more frequent, more distinctly dysenteric in character, and passed with tenesmus. Councilman and Lafleur were the first to describe the



ice in the stools during acute exacerbations of "small, opaque or ucent, gelatinous, greyish-yellow masses, varying in size from a pin's to a split-pea, which are fragments of necrotic tissue from the bases e ulcers, always containing amœbæ." These should be carefully t for. In an uncertain proportion of cases the bacillus of dysentery o met with in the fæces during the exacerbation. Charcot's crystals ometimes present in the stools. When the disease has gone on for time the general health becomes notably impaired. There is loss of te, loss of strength, loss of flesh, and anæmia. The digestion is ured. Undigested portions of food are passed in the stools. The ecomes dry and of an earthy colour, the tongue glazed, the feet kles œdematous. The emaciation in many cases is extreme. The s of the bones, covered with dry parchment-like skin, become ly distinct. The belly on either side is hollowed out, with the al column visibly projecting in the middle line. Unless an acute ation with sloughing, or some intercurrent disease or complication n end to the patient's sufferings, he dies of exhaustion. When y takes place, the amœbæ disappear from the stools, which assume atural appearance, and convalescence is slowly established.

some cases, when recovery has apparently taken place, small e remain in the bowel without giving rise to symptoms. These, s, form the foci from which amœbic abscess of the liver develops fter all trace of dysentery has disappeared. Sodré relates an e of a woman who passed amœbæ in her stools for twenty nd suffered from a muco-sanguineous discharge for four or five ery month, but was perfectly well in the intervals; the character amœbæ in this case is, however, uncertain.

**Complications.**—The most common complication of amœbic dysentery r abscess (*vide* p. 571). Perforation occurs most frequently in nous cases, but it also occurs in the insidious form of the disease. ; met with perforations in 12 out of 77 autopsies. The site of ation is the sigmoid flexure and rectum in half the number of (Bérenger-Féraud). Hæmorrhage to any serious extent is rare, and seldom the direct cause of death. Adhesions and displacements ing from peritonitis have already been noticed.

**Diagnosis.**—A diagnosis of amœbic dysentery cannot be conclusively ished from the discovery of amœbæ in dysenteric stools, for, as dinn points out, harmless amœbæ, as well as other protozoa, are present in bacterial dysentery caused by the Shiga-Flexner bacillus. erum test is, therefore, of value, and if negative, gives pathogenetic cance to the amœbæ. In chronic cases the course of the disease is characteristic. An intermittent diarrhœa, however mild, should ked upon with suspicion in the tropics, and lead to an examination, i need be, to repeated examination of the stools. When amœbæ all numerous, there is little difficulty in finding them in the fæces, stools be examined soon after being passed, and while still warm. ment of mucus or a drop of the liquid fæces is put on a slide, a

cover-glass placed lightly over it and examined with a medium power. In cold weather, the hot stage should be used. There is some risk in mistaking certain large granular cells described by Jürgens which appear to consist of an endo- and ectoplasm, and other objects present in the feces for resting amœbæ, and it is a safe rule not to make a positive diagnosis unless motile forms are observed.

**Prognosis.**—The case-mortality cannot be under 20 per cent, and sometimes is much higher. The prognosis should be guarded, however mild a case may appear. The intractable nature of the disease has also to be borne in mind. After apparent recovery relapses are apt to occur.

**Prophylaxis.**—The principal measures to be adopted for the prevention of amœbic dysentery may be summarised as follows: (1) The thorough disinfection and safe disposal of dysenteric stools, which are none the less dangerous when they become formed during a period of quiescence. (2) The substitution, when possible, of the water-carriage system for privies and cesspools. Where this is impossible the adoption of measures to prevent, as far as possible, the pollution of soil and water. (3) To secure a water-supply from a pure source, its filtration, and safe storage. When tanks and cisterns are in use the utmost care should be taken to protect them from contamination. (4) Thorough draining of the soil. (5) The boiling of water used either for domestic or drinking purposes. (6) The cleanly cultivation and scrupulous washing and, if need be, scalding of raw vegetables. (7) An easily digested, non-irritating diet, and the avoidance of excesses, fatigue, and exposure.

**Treatment.**—In the acute form of the disease, and during the exacerbations of the chronic form, the patient should be confined to bed. During the intermissions carefully regulated exercise, according to the requirements of each case, is beneficial. When acute symptoms are present, the diet should be restricted to milk, chicken-tea, barley-water, egg-albumin, beef-juice, and the like. In the more chronic forms, milk if it agrees with the patient, should still form the staple diet, but mild farinaceous foods and eggs may be allowed. Some cases do well on raw or half-cooked meat finely minced. Stimulants in small and frequent doses are necessary when prostration sets in.

For severe abdominal pains, poultices, turpentine-stupes, or hypodermic injections of morphine are to be resorted to. Small enemas of laudanum and starch are particularly useful in relieving the tenesmus when the disease is in the lower bowel. Change of climate is to be recommended in obstinate cases, but when the disease comes under treatment at the beginning, when the regular administration of enemas is so important, it is not advisable to send the patient at once on a voyage, as this gives the disease an opportunity of establishing itself before efficient treatment can be adopted.

It is only in cases of primary acute mixed infections that benefit can be hoped for from the use of ipecacuanha, and even in these its employment is of somewhat doubtful advantage. The safest line of treatment in this form is the use of eliminative and antiseptic remedies.

with large enemata when they can be tolerated. The sulphate of zinc in drachm doses every three or four hours, or castor oil twice a day, may be given along with benzo-naphthol or

If sloughing sets in, turpentine in small doses may be given in large or in larger doses along with castor oil. Large warm enemata of a strength of 1 in 1000 should be employed. The irritation and pain is sometimes so great that their frequent administration is difficult, but, when possible, they should be given two or three times in the twenty-four hours. I have sometimes found good results from boracic acid enemata, 10 grains to the ounce. These may be advantageously alternated with quinine enemata. Ford recommends 0.10 to 0.40 per cent solutions of eucalyptus gum as quite the most valuable drug for rectal use in the acute form of the disease. It may be given in milk, water, or a mixture of milk and olive oil. I have no experience of this remedy in the acute form, but it seems to deserve a trial.

Such difference of opinion exists as to the utility of internal remedies given by the mouth in the ordinary chronic form of the disease. My experience of ipecacuanha has not been encouraging, but others have found it useful. Sodré considers that, given by the Brazilian method (see p. 101), it gives the best and surest results. Birmingham found "that the symptoms in most cases responded promptly to the ipecacuanha in 3 to 4 gramme doses." Roemer was successful in three out of fourteen cases by the administration of a strong preparation of the decoction of simaruba and pomegranate root. Dr. Huntly found, in the case of his own child, that amendment followed drachm doses of a 1 in 10,000 solution of the perchloride of mercury; in some cases that have not reacted to calomel, as I have found frequent small doses of use. Kartulis gives three or four of a grain of calomel ten times in twenty-four hours for several days, for its amœbicidal action, either alone or combined with naphthalin, and he only had opportunity in Egypt of forming an opinion on the efficiency of the remedy. It is evident that these doses cannot be persisted in for a long time. Quincke gave calomel alone in the same dose at first, and then gradually increasing to four times a day. Calomel in small doses given two or three times daily does undoubtedly reduce the number of stools and improve their character, and causes a temporary disappearance of the amœbæ, but in my experience it seldom effects a permanent improvement. Most reliance should be placed on rectal medication. The most powerful substances are amœbicidal; but the difficulty lies in reaching the parasite by drugs administered by enema when it is burrowing under the mucosa. Hence the importance of early treatment, before the submucosa is extensively invaded. Prof. Osler speaks highly of the value of warm quinine injections of the strength of 1 to 5000, 1 to 2500, or 1000. Quinine is the drug most frequently employed, and the enemata are often satisfactory, especially when resorted to early. If the disease does not yield to solutions of the strength recommended by Prof. Osler, solutions of 1 to 750 may be tried. One and a half to two pints of the solution should be introduced slowly by gravitation

through a soft rubber tube passed well up the bowel. Quinine, however, even in strong solutions, frequently fails, and in this case recourse should be had to some other amœbicide. Harris obtained the best results by injecting about two pints, twice a day, of the ordinary solution of hydrogen peroxide, diluted with four to eight times its amount of water. This may be given on alternate days with quinine. Some, again, prefer permanganate of potassium, four to seven grains to a pint. Ford believes that no drug rivals eucalyptol in solutions of 0.05 to 0.20 per cent. in sterile water, or normal salt solution. Upon the appearance of an exacerbation he recommends that eucalyptus gum be substituted. I tried this with apparent benefit in one case, but it is still doubtful whether the cure is permanent. Enemas of nitrate of silver,  $\frac{1}{2}$  to 1 grain to the ounce, after the bowel has been well washed out, or sulphate of copper,  $\frac{1}{2}$  to 2 grains to the ounce, should be tried in obstinate and chronic cases, as recommended for chronic bacillary dysentery. Dr. Sandwith strongly recommends enemas of sulphate of copper with starch and opium from the outset, provided there are no symptoms threatening perforation.

Hæmorrhage is to be controlled by ergotin or adrenalin, or by ice applied to the abdomen. When perforation takes place, with general peritonitis, all that can be done is to relieve pain. Operative procedures will generally be out of the question.

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S. F.

### III.—OTHER DYSENTERIC AFFECTIONS ASCRIBED TO PROTOZOA

By ANDREW DAVIDSON, M.D., F.R.C.P. Ed.

**Spirillar Dysentery.**—Le Dantec has described a form of dysentery caused by a spirillum, not infrequently seen in the south-west of France, especially in and around Bordeaux, but which may prove to have a wider distribution. The spirillum, which has not been cultivated, is 6 to 12  $\mu$  in length and is readily detected in the mucus of the stools. A thin film of a portion of gray mucus from the fæces is fixed in alcohol-ether, coloured by dilute Ziehl solution, washed in water, and examined under an oil-immersion. The spirilla occupy the summits and interior of the epithelial cells, which they destroy, and in this way cause superficial ulceration of the mucosa.

The symptoms are those of a mild, non-febrile dysentery, which has never been observed to prove fatal, but which, if neglected or improperly treated, may persist for months. Le Dantec mentions a case, treated by bismuth, salol, tannin, pancreatin, and pepsin, which persisted for six months, but ultimately yielded to antiseptic enemas. This method of treatment speedily effects a cure in recent cases, but must be continued for a considerable time when the disease is chronic.

Spirilla are frequently met with in the tropics in the stools of patients suffering from bacillary dysentery without any reason for suspecting that they have any pathogenetic significance.

**Ciliar Dysentery.**—*Balantidium coli* (Fig. 80) belonging to the class of ciliata, measures from 70 to 100  $\mu$  by 50 to 70  $\mu$ . Strong has shown that it can give rise to a specific diarrhoea which occasionally terminates in ulceration of the large intestine. Dehio has collected sixty-one cases of this kind, but without doubt the parasite is a much more frequent cause of dysenteric symptoms than this indicates.

The symptoms of balantidium infection are those of a chronic catarrh ending in ulceration of the large intestine. In one of Dehio's cases, which proved fatal in six weeks, the disease began with vomiting, anorexia, wasting, diarrhoea, loss of strength, and the presence of balantidia in the stools. On autopsy, the intestine was found "diphtheritic" and numerous balantidia were found in the mucosa. As a rule, the disease runs a more chronic course, sometimes lasting for years. In a case recorded by Klimenko, quoted by Mr Jackson Clarke, the patient suffered from diarrhoea for three or four years, and passed balantidia in



ols. Quinine injections failed, the weakness increased, the face  
nbs became œdematous, and the patient died. At the autopsy  
lcers were found in the rectum, two in the transverse, and one in  
cending colon. In the ulcers only a few degenerated parasites  
ound, but the microscope shewed balantidia surrounded by in-  
tory infiltration in parts of the mucosa distant from the ulcers.  
described three cases, two of which proved fatal. In one of these  
as chronic catarrh of the large intestine but no ulceration.

e *Balantidium minutum* (Fig. 81) and *Nyctotherus faba* of Schaudinn  
2) are generally looked upon as non-pathogenetic, but the former  
n found associated with mucous diarrhœa.

e treatment offering the best prospect of success is that by enemas  
or other of the amœbacidal drugs—noticed under amœbic dys-

Methylene-blue in solutions of 1 to 3000, as recommended by  
ani, should be tried.

**gellar Diarrhœa or Dysentery.**—Cercomonads and trichomonads,  
ing to the *Flagellata*, may be met with in the stools of healthy  
, and are not necessarily pathogenetic. They are sometimes, how-  
resent in such large numbers, and associated with a diarrhœa which  
when they have been got rid of by treatment, that they must be  
upon as occasionally pathogenetic. Castellani records two cases  
ed in Ceylon apparently caused by flagellates—*Trichomonas hominis*  
*mbilia intestinalis* (vide p. 55). The stools in both cases were liquid,  
ownish colour, but did not contain blood or pus. Enormous numbers  
e parasites were present, and in one of the cases a few flocculi of  
were mixed with the fæces. There was no fever, griping, or  
us. The disease was not a true dysentery, although it is possibly  
nes so. A cure was effected by enemas of three pints of a 1 in  
olution of methylene-blue, given twice daily.

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A. D.

## SPRUE

By Sir PATRICK MANSON, K.C.M.G., M.D., LL.D., F.R.S.

**SMS.**—*Aphthoides chronica*, *Cacheria aphthosa*, *Chronic aphthæ*, *Chronic*  
*irrhœa*, *Chronic dysentery*, *Diarrhœa alba*, *White flux*, *Chronic enteritis*,  
*Chronic enteritis of warm countries*, *Aphthæ tropicæ*, *Aphthæ orientales*,

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*Stomatitis intertropica, Ceylon sore mouth, Indische sprue, Sprue, Appi*  
*or Athrepsie coloniale atrophique, Chronic or Endemic diarrhoea of Cokin*  
*China, Psilosis linguae et mucosae intestini.*

**Definition.**—Sprue or psilosis may be defined as an insidious, chronic, remitting inflammation of the whole or part of the mucous membrane of the alimentary canal, occurring principally in Europeans who are residing or have resided in tropical or subtropical climates. It is characterised by irregularly alternating periods of exacerbation and comparative quiescence; a peculiar, inflamed, superficially ulcerated, exceedingly sensitive condition of the mucous membrane of the tongue and mouth; great wasting and anæmia; pale, copious, and often loose, frequent, and frothy fermenting stools; very generally by more or less diarrhoea; and also by a marked tendency to relapse. Sprue may either be primary, or it may supervene on or complicate other affections of the alimentary canal. Unless properly treated it is usually fatal.

**Nomenclature.**—Some explanation is due for the introduction, or rather reintroduction, into medical literature of the name under which I propose to describe this disease.

Although the first describers of the complaint recognised its peculiar characters, and gave it special names,<sup>1</sup> more recent writers have dropped these, and, whilst still recognising the peculiar clinical and pathological features, describe them under such loose and wide terms as “chronic diarrhoea,” “chronic dysentery,” “tropical diarrhoea,” and so forth. This looseness of nomenclature I regard as a distinct misfortune as well as a retrogression; for, as a consequence, the student is led to overlook or to ignore the special characters of the disease, and has his attention directed, not to the condition itself, but to one only, and that not a constant constituent symptom of a complex pathological condition. The public, moreover, is likewise misled by such names. When the subject of this very serious disease is informed that he is suffering from chronic diarrhoea, he fails to appreciate the gravity of his position, and will not readily submit to a treatment which, to most persons, is a trying and prolonged ordeal. To tell him he is suffering from chronic diarrhoea is very much like telling the victim of cancer that he is suffering from “tumour”; he shirks and puts off a treatment which, did he but properly apprehend the danger, he would readily submit to.

The medical man, likewise, who encounters these cases for the first time is misled by these vague names, and it is only after more than one blunder and some years of experience, bought at the expense of his patients, that he begins to know the deadly nature of the complaint he is dealing with.

Lastly, the absence of a special name has led the writers of text-books and teachers to overlook a disease of which they themselves have had little experience in Europe, but which, nevertheless, is a common

<sup>1</sup> Hillary called it *Aphthoides chronica*; Latham, *Cachexia aphthosa*; Chisholm, *Chronic aphtha*.

well as a dangerous disease among Europeans in hot climates. Thus, young medical men land in the tropics, not only without experience, but also without information or guidance in a very important matter.

For these and similar reasons, I think that the adoption of some such distinctive and catching name as "sprue" for this disease is desirable.

Etymologically the word I adopt is not very defensible, but neither are many of the names in use in medicine—cancer, for example. At one time the word "sprue" was applied to what is now called "thrush" and "aphthæ", for years, however, it practically dropped out of the language, so that confusion is not likely to occur on this score. When my attention was first drawn to the subject, I found that the Dutch equivalent—"spruw"—was in universal use in Java to indicate this special form of tropical entero-colitis; and as the name had proved to be a very practical and suitable one there, I thought I could not do better than adopt it in a short notice of this disease I contributed many years ago to the *Medical Reports of the Chinese Imperial Maritime Customs*. I understand Dr. Henderson of Shanghai, recognising the desirability for a distinctive name, had also adopted this Dutch word. The name was quickly taken up by the profession and European public in China, where it is now well understood among the various foreign communities. It is the name employed in the nomenclature of diseases drawn up by the Royal College of Physicians of London (1906).

In consequence of the introduction of this name it would seem that the public, at all events in the East, is gradually becoming educated into some knowledge of the disease thus indicated, and I believe that in this way the hands of the physicians concerned have been strengthened. Not only so, but the profession in general is also becoming alive to the importance of the subject, and in time our knowledge of an interesting and very important clinical symptom group will be extended. These considerations seem to me sufficient justification for the adoption of the word "sprue," and for persevering in its use.

"Psoriasis" (ψῑλος, 'bare') was suggested by Thin in one of his valuable papers as a substitute for "sprue." It is expressive of the fact that bareness or rawness of the mucosa is a leading feature of the complaint. The word is certainly more scholarly than "sprue," but, at the same time, like "diarrhoea," it is but partially descriptive, and therefore misleading. Moreover, I think it is less likely to become popular. It has the advantage of forming an euphonious adjective—psilotic, signifying bare, stripped, or raw, in which sense I shall use it of mucous membrane.

**Literature.**—The earliest, as it is one of the best and most graphic descriptions of what I would call the protopathic form of sprue, we owe to Hillary (1776). Since he wrote, most systematic writers on tropical diseases have dealt with the subject, I may mention Annesley, Twining, Martin, Grant, Goodeve, Donald, Moore, Chevers, Doutroulau, Corre, Kelsch and Kiener, and many French writers. Sir J. Fayrer gives an excellent clinical account of it. Among the more recent contributions to the subject I may mention papers by myself, by C. L. van der Burg, and

Thin's well-known articles. Up to the date of its publication (1887), the most exhaustive work on sprue is that by Bertrand and Fontan, in which, in addition to much valuable original matter, there is an excellent summary of the considerable French literature on the subject. Still more recently we have important papers from Musgrave, Bassett-Smith, Maurer, Richartz, and van der Scheer.

**Geographical Distribution.**—Although sprue is very much more common in some parts of the tropical world—Java and Cochin China, for example—than in others, there is good reason to believe that it occurs occasionally in most tropical countries, if not in all. Many of the cases called “chronic diarrhoea” or “chronic dysentery,” coming from the West Indies, from tropical America and from Africa, answer in their descriptions to sprue. Hillary and Chisholm certainly encountered it in the West Indies. There can be no doubt about its frequency in India, Ceylon, the Malay Archipelago (Burg and others), the Eastern Peninsula (Bertrand and Fontan and many others), Mid-China, and especially in South China and Manila. Though most common in the tropics, it is not strictly confined to these regions; it is not infrequently met with in Shanghai, and in the European settlements on the Yangtze River, many degrees to the north of the tropics. It occurs in Japan; I have treated well-marked examples of the disease from that country. Although its development and rapid progress seem to be favoured by the perpetual summer and damp heat of such countries as Java and Cochin China, yet a dry, bracing climate, such as Shanghai and the greater part of China enjoy during several months of the year, is not sufficient to ensure immunity from a disease which is apparently provoked by the great heat and relaxing influences of a long and trying summer. Speaking from my own experience in South China, where the winter climate is very fine, of all the *chronic* diseases the European has to contend against there, sprue, in its various forms and degrees, is by far the most frequent as well as the most formidable.

**Etiology.**—Amongst the remoter causes of sprue prolonged residence in hot climates must be reckoned as the chief. In certain instances the disease shews itself after a residence of one or two years only, or even less. This, however, in my experience, is a rare occurrence; usually I find that the victim of sprue has resided in the tropics for many years.

As more direct factors may be enumerated exhausting diseases, particularly those of the alimentary canal, such as dysentery, diarrhoea, hæmorrhoids, fistula in ano, the morning diarrhoea of the tropics—an affection which must not be confounded with the morning diarrhoea of alcoholism—child-bearing, miscarriages, and other uterine troubles, particularly those attended with hæmorrhage, prolonged lactation, syphilis, courses of mercury and iodide of potassium, bad food and water, mental anxiety, chills, and so forth. Malaria has, of course, been cited as a cause of sprue; I cannot say, however, that there is much evidence for this. Nor can it be said that bad or insufficient food is a very potent factor, for the disease is common enough in places—Shanghai, for

ple—where the food market cannot be surpassed; moreover, it is quite as prevalent among the rich as among the poor.

Of the actual cause of sprue nothing is known; we cannot even say whether it be of a physio-pathological character, or a specific germ. At the time the discovery by Normand of the parasite which Bavay called *millula stercoralis*—since proved to be the free form of *Rhabdonema tinale*—in the stools of cases of Cochin-China flux, gave rise to the opinion that sprue was a helminthiasis similar in some respects to ankylostomiasis. This hope has been abandoned, as in many cases these parasites are entirely absent. According to Musgrave *Amœba coli* is often present in the stools, and in 7 out of 16 cases the blood (dilution 1 in 10) gave a positive agglutinating reaction with cultures of *Bacillus dysenteriae*. Though it is possible that one of the innumerable species of bacteria present in the stools in sprue may be the cause of the disease, such a relationship has not yet been proved. It was observed by Thin that in some of his cases the stools, particularly during the exacerbations, contained almost a pure culture of a particular species of bacterium. These similar concurrences are facts to be noted, but no definite conclusions can be drawn from them.

In connexion with the etiology of sprue it is of importance to bear in mind that whatever the actual cause may be, it is something which can remain latent for a considerable time. An individual who has lived in a sprue country may return to Europe apparently in good health, and remain so for months or even for years, and yet after this interval the disease may shew itself for the first time. Or a patient may recover from the disease, and yet, without leaving England, may suffer a relapse after months or years of good health. The capacity for latency is as of so many tropical diseases is very remarkable. Van der Meer makes a valuable suggestion, based unfortunately on one observation only, to the effect that the presence of latent sprue might be suspected if excess of fat be detected in apparently normal or in abnormally pale subjects. The presence of the latent disease would clearly indicate the necessity for care in diet, etc.

**Pathology and Pathological Anatomy.**—Owing to practical difficulties in examining a structure so delicate as the mucous membrane of the alimentary canal, and to the fact that in a disease so chronic the primary and essential features of the complaint become overgrown and obscured by secondary changes, it has hitherto been found impossible to ascertain the primary and fundamental lesion of sprue. It seems to me that more information is to be got on this point from a study of the lesions of the tongue and mouth in the early stages than from the study of the lesions of the other parts of the alimentary canal in the later stages of the disease. If the tongue be a trustworthy index of what is going on in the upper and lower parts of the alimentary canal, then we must conclude that the primary lesion, at all events the one first appreciable by the unaided senses, is a catarrhal state of the mucous membrane as evidenced by premature shedding of the epithelial covering, congestion of the papillæ,

and folliculitis going on to superficial ulceration. What in its turn may be the cause of this catarrh we cannot say.

Whether it be in consequence of this hidden, unknown primary cause, or of the catarrh which it induces, it is very certain that in sprue digestion and assimilation are early affected; and that this, in no very long time, leads to tissue starvation. To this tissue starvation, doubtless, is attributable not only much of the general wasting but many of the special symptoms referable to the alimentary canal. Dr. D. D. Cunningham, in a very able paper on the effects of starvation on vegetable and animal tissues, has shewn that the effect of starvation in Indian famines is not only to cause a loss of bulk of the tissues generally, but also, if the starvation be carried beyond a certain point, to actual destruction of tissue. Particularly is this the case with the mucous membrane of the alimentary canal, in which, in famine, an actual and irreparable destruction of secreting and absorbing tissue is apt to occur. As a result of this destruction, when sufficient food is at last supplied, as in famine camps, digestion and absorption, owing to actual loss of the necessary tissues, cannot be effected; thus, so far from proving a benefit to the starving, good food and plenty of it does but precipitate death, inducing by its mechanical and chemical effects further irritative changes in the starved and eroded bowel. In this way is brought about the diarrhoea and dysentery of famine camps, and many of the diarrhoeas and dysenteries of the half-starved populations of Eastern countries who, in too many instances, live in a state of chronic famine—a state hardly conceivable by the fortunate populations of more favoured countries.

Doubtless something analogous to this famine diarrhoea and dysentery occurs in sprue; an artificial physiological famine is induced. Therefore, in contemplating the lesions found after death in a case of sprue, we must be careful to bear in mind that many, if not most of them, are not the specific and primary lesions of sprue, but the primary and secondary effects of starvation. Thus, when at the end of a long case the alimentary canal is examined, there is present a threefold pathological condition, namely—(a) the specific and primary lesion, (b) the specific starvation lesion, (c) the secondary irritative lesions. To sort out these in the present state of pathological knowledge would be an impossible task. Very few post-mortem examinations have been recorded with the thoroughness and minuteness of histological detail necessary to enable us to carry out such an attempt successfully.

After death from sprue the tissues as a whole are found to be abnormally dry, in consequence of which the body tends to mummify rather than to decompose. The thoracic and abdominal viscera are both actually and relatively wasted. Tuberculous foci may be found in the lungs. In the liver there are no morbid appearances which, from their invariable presence, might be considered essential. More frequently, according to Bertrand and Fontan, certain changes are encountered in the pancreas, isolated lobules of which shew signs of parenchymatous change—such as fatty or granular degeneration of the cells, with softening of



ini and slight inflammatory infiltration of the connective tissue. Pancreatic changes, however, are probably secondary and not local, as, like those sometimes found in the liver and also in the spleen, they are far from constant.

As might be expected, the principal changes are to be found in the alimentary canal, part or the whole of which, including in many cases the appendix, is invariably found to be diseased. Speaking generally, the canal may be described as being thinned to such an extent as to be parchmentous. There is no necessary or notable lesion of the serous or muscular coats; but from mouth to anus, either in segments or in patches of greater or less extent, or universally, the mucous membrane is diseased. Its free surface is coated with a thick layer of dirty, viscid, tenacious mucus. On washing this away the mucous membrane is found to present a number of lesions:—1st, congested patches; 2nd, inflamed patches; 3rd, ulcerated patches; 4th, pigmented patches; 5th, thin-scarred, cicatricial patches; 6th, absence or wasting of the mucous glands; 7th, in addition to these the mucous membrane, where entirely replaced by fibro-cellular cicatricial tissue, is felt and seen to be strewed with minute spherical tumours—about the size of a pin's head—surrounded by a dark pigmented areola. These little nodules, on being cut into, are found to be situated in the submucosa, to have gelatinous contents, and generally a lateral or central punctiform orifice. They are mucous cysts replacing follicles (47).

Under the microscope, sections of the diseased portions of the œsophagus, stomach, and intestines shew patchy or general destruction of the surface of the mucosa in all degrees from slight erosion to complete disintegration of the villi, glands, and follicles; effusion into and rupture of the closed follicles, leading to the formation of mucous cysts or abscesses which subsequently rupture and ulcerate; infiltration of leucocytes of the basement membrane; and inflammatory effusion into the submucous layer, with subsequent fibro-cirrhotic changes in the connective tissue.

The mesenteric glands also are generally enlarged, dark, and perhaps indurated.

The ulceration met with is not always extensive. In the stomach and upper parts of the alimentary canal the sores are generally very minute and superficial; towards the end of the ileum and in the colon the ulcers may be deeper, and associated with some thickening of the bowel from inflammatory effusion.

In speaking of the changes in the stomach, Bertrand and Fontan say, "The stomach may be completely destroyed by embryonic cell proliferation in the villi on the one hand, and by ulcerative folliculitis on the other. . . . It presents sclerosed and pigmented portions which are probably the ultimate stage of the nutritive and circulatory troubles." Thin sections of the ileum in a case he records, "The mucosa was almost entirely destroyed, being replaced by a structureless substance enclosing the crypts, and here and there the remains of a follicle. . . . The sub-

mucosa appeared much thickened, and the fibrous tissue abundant and more than usually solid in consistence. The walls of the vessels were also thickened, altogether denoting a more chronic process than in the other parts of the intestinal canal."

If I may venture to interpret these morbid appearances I would suggest that, as the primary lesion in the alimentary canal in sprue is one from which recovery is possible, and as most of the lesions of the stomach and ileum just described are of such a character that recovery from them is impossible, these latter may be regarded as a result, but not the necessary result of the primary lesion—not essential features of the disease. The primary pathological condition of the mucous membrane, seeing that it admits of recovery, is probably of the nature of a catarrh, and confined to premature shedding of epithelium and folliculitis; this view is further borne out by what is seen in the mouth. After a time, this condition being unrelieved, more serious changes may supervene; the necrotic famine changes, or inflammatory changes induced by persistent irritation, may set in. Either or both of these may lead to ulceration on the one hand or to cirrhotic changes on the other; and in one or both of these ways the mucous membrane is changed into scar tissue without glands or absorbents, gradually becoming useless as an agent in nutrition.

Applying the revelations of the post-mortem room to the interpretation of symptoms, we can understand that according to the region and extent of the alimentary canal involved will the symptoms be. If the œsophagus be implicated, dysphagia and substernal burning will be prominent symptoms; if the stomach be involved, vomiting and dyspeptic troubles of various kinds will occur; if the small intestines, lenteric diarrhoea; if the colon, dysenteric diarrhoea. All of these conditions and symptoms may and often do combine in one and the same case.

The frequent presence of ulcers in the colon has given rise to much discussion, some observers contending that they are conclusive evidence of the dysenteric nature and origin of sprue. But it is evident from a study of the history of the evolution of this disease that, in a large proportion of cases, the progress of the pathological process is from mouth to colon, and not from colon to mouth. The psilotic process is a distinctly different one from the dysenteric process, although they may and frequently do concur. True dysentery may in some instances be the starting-point of sprue.

Interesting features in sprue are the absence of the normal yellow tint in the stools, the phenomenal bulk of the stools, and the presence in them of large quantities of gas. The gas is doubtless the result of decomposition of bacterial origin, and the bulk partly the result of the spongy structure of the faecal mass from the infiltration of it, as can be recognised by the microscope, with minute bubbles of this gas, and also by the presence of undigested particles of food, more especially fat and fatty acids. Analyses by Wynter Blyth, Martin, and van der Scheer all concur in this, and it may be taken as an established fact that in sprue the absorption of fat is defective. The same observers concur in their

explanation of the pale colour of the stools. Bile pigment and bile acids, though at times absent (van der Scheer), are generally present and recognizable, both chemically and spectroscopically; but for some unknown reason the greater part of the bilirubin, the essential colouring agent of normal feces, has undergone reduction into a colourless substance, the leucobilin of Nencki. Bertrand and Fontan's observations on the implication of the pancreas may have a bearing on this question, seeing that hydrobilirubin, the cause of the colour of healthy feces cannot, according to Walker, be produced from the bile without the aid of the secretion of the pancreas.

The absorption of the nitrogenous elements of the food and carbohydrates, though defective, is not nearly so much so as in the case of the fats. The acidity of the stomach varies in different cases and in the same case from time to time; in some cases at certain times there may be complete achlorhydria, but it cannot be said that there is any manifest and constant correlation between the general symptoms and the gastric acidity.

Pending further investigation I regard sprue, etiologically, as a specific disease predisposed to by the influences of meteorological conditions present in hot countries on certain constitutions; further, I believe that in many instances it arises without other and more special predisposing influences, but that in a large proportion of cases it is favoured by antecedent pathological conditions, over and above those induced by climate simply, chief among these are dysentery, catarrhal diarrhoea, hepatic disturbances, and other morbid states, more particularly those connected with the alimentary canal. Pathologically, I regard sprue as a morbid process specifically distinct from true dysentery, and consisting in a specific, chronic, catarrhal condition of all or part of the digestive tract which, if it persist, leads in time to necrotic and inflammatory processes in the mucosa ending in destruction and permanent loss of glandular and absorbent structures, and so to what in a certain sense might be called physiological starvation.

**Symptoms.**—Insidiousness, chronicity, improvement and relapse, and slow progress on the whole are characteristic of the evolution of this disease. The leading symptoms, when it is thoroughly established, are—

1. Irregular action of the bowels.
2. The passage of phenomenally copious, pale, drab-coloured, yeasty-looking, sickly-smelling stools.
3. Tenderness and often great soreness of the tongue, buccal mucous membrane, fauces, and sometimes of the gullet, depending on a complexity of surface lesions including (a) denudation of the epithelium of the mucous membrane generally; (b) the formation of minute herpes-like vesicles, single or in groups, with an inflamed areola, which quickly rupture, leaving (c) small, superficial but exquisitely tender, ashen grey erosions or ulcers; (d) larger, inflamed, bare, slightly-eroded patches, smooth on the surface usually, or with a slight muco-purulent covering

where in contact with the teeth—as on the inside of the cheeks or lips; often, when on the soft palate, they are markedly granular, probably from inflamed follicles; (e) congestion and swelling of the fungiform papillæ, especially about the tip and edges of the tongue; (f) superficial cracks on the dorsum and edges of the tongue; (g) during complete remission of the acute symptoms, as happens occasionally in most cases, an atrophied state of the entire body of the tongue; this organ then appears pale and almost cartilaginous, with a smooth, glazed surface as if coated with varnish, and completely denuded of papillæ.

The erosions referred to, sometimes amounting to superficial ulceration and much sodden by the constant action of the saliva, are most frequently found under the tongue by the sides of the frænum, inside the lips and cheeks—especially where in contact with the teeth, and on the soft palate. The vesications ending in the minute grey ulcers are commonest about the tip and edges of the tongue; they come out in successive crops. Activity of both of these lesions is usually associated with increase of diarrhœa. In severe cases what I would call the “psilotic” condition of mucous membrane seems to extend through the entire length of the alimentary canal, affecting the pharynx, œsophagus, the anus, and, in women, even the vagina.

4. Dyspeptic conditions associated with the formation of large quantities of intestinal gas and acidity.

5. Pearly conjunctivæ; a dry, harsh, earthy-looking skin more or less deeply pigmented.

6. General wasting, usually including marked diminution of the area of hepatic dulness.

7. Anæmia and great physical and intellectual debility; and, especially in the advanced stage, querulousness and irritability of temper.

If we inquire into the history of a patient presenting these symptoms, we shall probably learn that he has been ailing for several months, perhaps for years; and that his symptoms began in one of three ways:—(a) Insidiously: he will tell us that before his disease definitely declared itself he used, without apparent reason, to be troubled with soreness of the mouth, attacks of flatulent dyspepsia, irregularity of the bowels, and, especially, a tendency to diarrhœa—often of pale, copious, frothy stools—in the early morning or during the forenoon. By degrees such attacks became more frequent, the mouth oftener sore, and the dyspepsia more troublesome. Ultimately this state became permanent, his strength and flesh began to decline, and, at last, a condition of confirmed invalidism was established. (b) Suddenly: being at the time in apparently good health—possibly after exposure, chill, fatigue, bad water, bad food, dietetic excess, or some other indiscretion—the patient was suddenly seized with profuse diarrhœa. After a time, the urgency of the diarrhœa subsiding, a degree of looseness and irritability of the bowels was left and became permanent, the stools gradually losing their yellow or brown colour and becoming pale and fermenting; and the tongue, from being thickly coated, being at first abnormally clean with a liability to the formation

and the edges and tip of small painful ulcers, and, ultimately, taking the psilotic character. The other symptoms of confirmed sprue were usually and simultaneously evolved. (c) Secondly: the patient had emerged from well-marked dysentery, which had merged into the chronic form, attended with the passage of three or four ill-smelling, mucoid, but not bloody stools daily. After several months or, perhaps a year or more of this, the mouth began to lose its natural fur, and to be bare or raw; flatulent dyspepsia with much distension after eating became troublesome; the stools got more massive, paler, yeasty-looking; and, ultimately, this condition becoming chronic, the dysenteric element gradually ceased to be the principal feature in the clinical picture, giving place to the characteristic symptoms of sprue.

These I consider to be the principal types of sprue. There are others, doubtless; the various combinations and degrees of severity and rapidity in the development of the leading symptoms are infinite. From what I have gathered, I consider that in China the form of sprue most frequently met with is the protopathic form; in Java the same seems to be the case; but in Manila, Cochin China, India, Africa, and the West Indies it would seem that in a large proportion of instances the disease is secondary to acute catarrhal enteritis, to dysentery, or to the affection called "hill-bill diarrhoea" (*vide* p. 567).

Forms of imperfectly developed or nascent sprue are common enough in the tropics. Sore mouth, with or without morning diarrhoea (sometimes of bilious stools, sometimes of pale fermenting stools), is a common affection among foreigners in the East, and, if ordinary prudence be exercised, may not go farther or seriously affect the health. Sometimes, indeed, tenderness of the mouth, burning of the tongue or gullet when acid, alcoholic, or pungent foods or drinks are taken, or, perhaps, minute ulcers followed by equally minute aphthous ulcers giving rise to actual soreness of the mouth, are the only symptoms present, even in cases with cachectic features. I once watched a case of this description during several years. The patient had resided for many years in the tropics, and on the whole had enjoyed good health. The only serious exception to this was an attack of dysentery many years before the appearance of the troubles for which I was consulted. Ever since the dysentery, however, attacks of sore mouth had supervened from time to time, being excited more particularly by nervous shock or similar physiological influences. The last attack had been unusually severe and protracted, and was accompanied by great wasting of a semi-cachectic kind, but there was no diarrhoea. It was only by careful dieting during many months that the psilotic condition of the mouth, and probably of the stomach and the upper part of the alimentary canal, was overcome, and the general state of the nutrition improved. Had this case been neglected or wrongly treated, doubtless, in a very few months, diarrhoea of pasty, fermenting stools would have supervened and ultimately passed into confirmed sprue.

Just as in this case, although the tongue lesion was very well



marked, diarrhœa was at no time a feature of the complaint, so in others, as pointed out by Bertrand and Fontan, diarrhœa and wasting of a characteristic type may exist, and yet the tongue retain its epithelium and be free from the erosions and inflamed patches so typical of sprue. Indeed, these writers seem inclined to minimise the significance of the psilotic condition of the mucous membrane of the mouth as an index of the condition of the remainder of the alimentary canal. It must be admitted, however, that the morbid process in this disease may be patchy in its distribution, and that it may be confined to the lower part of the bowel, the higher part of which the tongue more particularly serves as an index—remaining healthy.

In many cases the soreness of the mouth is exceedingly troublesome, only the very blindest fluids can be tolerated. Even the movements of deglutition may be excessively painful, yet they are constantly provoked by the salivation induced by the state of the mouth. In other cases the mouth—especially during sleep—becomes very dry, the tongue literally so cleaving to the roof that to get it moistened and liberated every morning is quite an operation. Many complain bitterly of a feeling of soreness and burning in the chest, always aggravated by food—doubtless depending on erosion of the œsophageal mucous membrane. Hunger, too, sometimes amounts to acute suffering, and, as with diabetics, may lead to strange moral perversions. I have seen cases in which the constant craving for food brought on a hysterical condition in which the patient, provoked by some savoury smell, and throwing prudence to the winds, rushed to table and indulged indiscriminately in the family meal. Thirst, too, may be a troublesome symptom. So may be distension of the abdomen from flatus and accumulated food: a smart attack of diarrhœa affords welcome relief in such cases. Sleeplessness is often complained of. In sprue the temperature is below normal, and the patient's feet are often painfully cold; just before and during an exacerbation of symptoms there may be a rise of one or two degrees in the body-temperature, at other times it is subnormal. As the disease progresses both the number and value of the red blood corpuscles diminish, the relative proportion of the white increasing. At recovery sets in this is reversed. The quantity of urine passed is in inverse proportion to the diarrhœa.

When sprue has become thoroughly established, unless a proper course of treatment be adopted and persevered in for months or perhaps years, the disease as a rule becomes gradually worse,—slowly, it may be, but on the whole none the less surely. Temporary improvements are followed by relapses: the slightest dietetic indulgence, exposure to wet or cold, fatigue, mental depression, and such like occurrences, are nearly sure to bring about a fresh attack of diarrhœa and an aggravation of the morbid symptoms. So the case gradually goes from bad to worse, emaciation becomes extreme, and the dusky, dry, unhealthy, earthy looking skin hangs in loose folds on a skeleton every bone of which can be counted. The belly, which on palpation feels soft and doughy, as if the abdominal



were abnormally thin and toneless, alone is filled out; it is generally filled by accumulated gases, and the gurgling and movement of gas can be seen, heard, and felt. The liver, in harmony with the wasting rest of the body, is shrunk to abnormally small dimensions. Sometimes a trace of albumin may appear in the urine. Finally the mouth is covered with mycotic thrush, feet and ankles swell, and the patient, if not suddenly killed by an attack of choleraic diarrhoea or intercurrent acute disease, dies slowly of starvation.

If proper treatment be adopted in time and before the mucous membrane has been so extensively destroyed as to be unfit for digestion, should the patient have not yet entered upon the vicious pathological process described above, the diarrhoea will cease, and the psilotic state of the mouth subside, to recur in milder form and at longer intervals until it appears for good, and the stools will gradually regain their proper form—at first, perhaps, in a fitful sort of way, one part of a motion properly coloured whilst the remainder is still pale. By degrees the patient gains flesh, and, finally, when he recovers the power of digesting a fairly liberal diet, his muscular and intellectual powers will be restored. For a long time, however, looseness of the bowels, slightly inflamed mouth, and flatulent dyspepsia may recur on the smallest provocative symptoms shewing that the disease, although apparently cured, is still lumbering.

Occasionally it happens that careful treatment, by checking the more violent symptoms, gives rise to a deceptive arrest of the disease; the frequency of the mouth ceases to recur, and diarrhoea is in abeyance. Notwithstanding this, nutrition does not improve; the food the patient adds nothing to his weight or strength, both of which gradually decrease, without any very manifest reason, as in diseases like cancer or chronic anæmia. In all such cases it will be found that the stools are unusually large. Doubtless too large an extent of mucous surface has irretrievably been destroyed, and absorption does not balance waste. In such a case the right treatment has come too late.

**Treatment.**—This is mainly dietetic and hygienic. If carried out gently by the physician and conscientiously by the patient, and if instituted at a sufficiently early period of the disease, it is generally thoroughly successful. On the other hand, if treatment be wrongly directed, carried out in a half-hearted way, or too long postponed, recovery becomes an impossibility.

In prescribing a treatment for a case of sprue, the pathological condition of the bowel must always be present to the physician's mind; first never forget the eroded and tender mucous membrane, the weakness of glandular structure and villi, and the liability of food in the presence of the digestive and absorbing capacity to decompose and irritate. The indications demanded by these things are clear and distinct. They are, first, to place the inflamed gut, so far as is possible, in a state of absolute rest; secondly, to supply a food of as bland a nature as possible; and, thirdly, a quantity of food no greater than can be dis-

posed of by the digestive juices and absorbing apparatus. For the fulfilment of these indications what is known as the "milk treatment" is incomparably the best.

When a diagnosis of sprue has been arrived at, it becomes the duty of the physician to endeavour to secure the co-operation of his patient by impressing upon him the great danger of procrastination, the deadly and insidious nature of the malady if neglected, the comparative certainty of recovery if promptly attended to. The conviction of the patient in this sense, and his or her hearty and intelligent co-operation, are the first and most necessary steps towards a cure. Few, unless they have had actual experience of these cases, can understand the importance of the moral element in their management. Next in importance to this is the acquisition of a thorough knowledge of what the patient's alimentary canal can and cannot do. This knowledge can be gained only by a daily visit to the patient, and a daily inspection of the stools; and these daily visits and inspections should be kept up until the slow process of regeneration of mucous membrane has well set in, and the patient has become thoroughly educated in his own management. There must be no temporising, and in the event of relapse, no matter how trifling apparently in character, there ought to be no hesitation in harking back at once to special diet. To some readers it may seem a matter of supererogation to write of these things; but they are really, though so simple and self-evident, among those simple and self-evident things which, though of prime importance, are so generally overlooked and neglected.

When a patient has consented to undergo the milk treatment for sprue he ought to have clear directions how this is to be carried out. These directions are best given in writing, somewhat as follows:—

- 1st, Clothe warmly in flannel. If diarrhoea be active go to bed in a warm room, and remain in bed until the stools become solid.
- 2nd, Place a pad of cotton over the abdomen, keeping it in position by a broad flannel bandage somewhat firmly applied.
- 3rd, Stop all food and drink with the exception of three pints of milk per diem, the milk being taken in divided doses at intervals of one, two, or three hours, allowance being made for a reasonable amount of undisturbed sleep.
- 4th, The milk, warmed in cold weather, must not be drunk, but sipped with a teaspoon or sucked from a feeding-bottle.

It is generally desirable to commence the treatment with a teaspoonful of castor oil, and to repeat this for a time about once or twice a week, or whenever the stools become copious, frothy, or stinking.

As a consequence of this treatment, even in cases in which diarrhoea has been present for months or even years, the motions gradually diminish in number and amount, and increase in consistency. Usually before a week has passed they become solid; at the same time the soreness of the mouth diminishes, and the feelings of dyspeptic discomfort vanish. If, however, after two or three days there be no improvement in the diarrhoea, the quantity of milk must be diminished by ten ounces a day until

a minimum of 25 ounces is taken. Of course this is starvation diet; it must, not be persisted in too long, and the patient must be kept at absolute rest, and carefully watched and tended by an intelligent nurse.

After the motions have become solid, and have so remained for three or four days, the allowance of milk is increased by ten ounces daily until 100 to 150 ounces are consumed. Should the motions at any time become loose, this must be looked upon as an indication that more milk is being swallowed than can be disposed of, the daily quantity must therefore be correspondingly reduced, by half a pint at a time, until the stools again become solid. It should then, after three or four days, be cautiously increased once more.

By following this system, in nine cases out of ten the improvement is marvellous. Not only does the diarrhoea cease, but the dyspeptic troubles subside, the soreness of the mouth and gullet disappears, and the patient's condition improves in every respect. There may even be a gain in weight when the allowance of milk has risen to five or six pints. But, arrived at this stage, the troubles of the physician begin. The patient is very hungry and clamours incessantly for more substantial food. The friends, too, importune on his behalf, and often do not hesitate to accuse the physician of starving his patient. All this must be steadfastly resisted, however, and for at least a month—better for six weeks—the only answer to the incessant demands for more nourishment must be, "Milk only—nothing but milk." If the physician be so weak as to concede something prematurely he is pretty sure to regret it. Additional diet too soon begun means recurrence of diarrhoea, sore mouth, renewed wasting, loss of time, and, perhaps, loss of the last chance of recovery.

When procurable, an important and often most effective addition to the milk is strawberries. I have now many times seen their liberal use bring about the cure of what appeared to be almost hopeless cases. I have very seldom seen them disagree. They sometimes act so promptly as to suggest specific virtues. In every case they should receive a trial. The safest plan is to begin with three or four with each feed of milk. If found to agree as much as three or four pounds may be consumed in the twenty-four hours. The introduction of the strawberry I regard as the most important practical advance in the treatment of sprue since the formulation of the milk treatment.

Experience, and one or two trials carefully made, will tell us when to begin to improve the diet. An egg beaten up with milk may be tried in the first instance, and, if found to agree, made a permanent addition to the daily allowance of milk. Then some well boiled arrowroot or corn starch, or plain rusks, or plain biscuits, or some other simple form of farinaceous food may be carefully introduced. Bread is not well borne unless in the shape of bread and milk. Bananas or apples I have found to be well borne, and are often a very acceptable addition to the dietary; they must be given tentatively at first, and only in very small quantity, and be thoroughly masticated. If they are well borne, after a time as many as five or six may be taken daily. Then chicken broth may be

added in small quantities; afterwards fish, chicken, potatoes, sweet-breads, and so on. Beef and mutton, hot soups, fibrous vegetables, nuts, pastry, etc. are very badly borne, even for years after all symptoms of sprue have subsided, and it is frequently necessary in such patients to interdict their use altogether.

During convalescence, and for a long time thereafter, the patient ought to be instructed that on the slightest recurrence of sore mouth, or of the familiar feeling of dyspeptic discomfort, or of bulky, stinking stools, he should at once act on the hint, take a teaspoonful dose of castor oil or of compound rhubarb powder, starve for some hours, and then go on milk for a day or two, until the threatening attack of muco-enteritis has quite subsided. He can then resume his former diet. Prompt treatment of this sort on the threat of relapse saves weeks of discomfort, and perhaps averts a serious recurrence of illness.

Until the patient is taking at least a hundred ounces of milk a day he ought to keep his bed. Afterwards, when he gets up, he must be careful to clothe very warmly, to avoid cold, damp, fatigue, excitement, and everything leading to physiological strain of any description. Getting wet or feeling cold is most prejudicial to such patients; accordingly, when the winter comes round, he should, if possible, move to some warm and sheltered place in the south of England or to the Riviera.

As regards drugs, my own experience has been that they are very secondary matters, and, with the exceptions I have mentioned, may generally be dispensed with. If there be special indications, such as malarial fever or cachexia, appropriate drugs, such as quinine, may be demanded. When diarrhoea is very brisk, so that it is to be presumed that the violent peristalsis of the gut is interfering with any healing process that may be going on, then a few small doses of laudanum or of Dover's powder may be given; but it is a very great mistake to try to shut up the bowel altogether by sedatives or astringents. The gut should be regarded in the light of a surgical drainage-tube to be kept patent; the retention of a mass of putrefying material in the abdomen cannot possibly be of any advantage in the long run, or in any way conduce to recovery.

It sometimes happens that after a week or two of careful milk dieting, the stools, although diminished in number, fluidity, and quantity, are still deficient in consistency and unformed. Diarrhoea, in the usual sense of the word, has ceased; but the complete dehydration of the motions by the last part of the alimentary canal is not thoroughly effected; apparently there still remains a mild chronic catarrh of the colon. In this case a dose of laudanum is sometimes followed by solid stools. If this fail I recommend the injection per anum through a long tube (after washing out the bowel with warm water) of forty ounces of nitrate of silver solution—one-half to one grain to the ounce of tepid distilled water. This is often followed by solid stools. It is of no use, however, to give laudanum or to wash out the bowel in this way until there has been at least a fortnight of careful dieting. When the stools

ery loose and watery it does no good ; properly timed, these measures are often successful.

Much suffering is frequently caused by the raw state of the mouth. To mitigate this as much as possible the mouth should be rinsed out, at a time after taking milk, with water or a weak solution of borax. Rubbing the painful spots with a 5 per cent solution of cocaine, or with a solution of nitrate of silver or sulphate of copper, gives relief. I have found the following mouth-wash useful in such circumstances:—*Ol. creosoti* ℥ 1, *Tinct. pyrethri* drs. 4, *Tinct. myrrhæ* drs. 2, *Tinct. kramerizæ* ℥ 1, *Aq. camphoræ* to ounces 8 ; a teaspoonful in one or two winefuls of water.

When patients must have a mixture, the following, recommended by Squire, may be prescribed:—*Magnes. sulph.* grs. 8, *Tinct. rhei* ℥ 10, *p. zingib.* ℥ 10, *Aq. dr.* 1, to be taken three times a day. I have found no good, but rather the reverse, from bismuth, oxide of zinc, acetate of lead, nitrate of silver, sulphate of copper, and the vegetable astringents. Similar remedies designed to act as sedatives or astringents. It is probable that carbolic acid, salol, naphthol, cyllin, and similar antiseptics may be of service, but I have no specially favourable experience of their use in these cases. When diarrhoea has ceased, *nux vomica* may be given. I use often with advantage in these cases *injectio ferri arseni-hypoderm.* (Squire) in 15-minim doses every second or third day. The bael fruit is greatly extolled by Sir J. Fayrer, and is much employed in India in these and kindred cases. I have seen no benefit from the official extract.

Constipation should be systematically relieved by enemata of warm water, or, better, of linseed tea, or weak barley or rice water.

In cases of dysenteric origin, after milk diet has been thoroughly rejected out for a fortnight with partial success, nitrate of silver enemata, as first described, may be required. Sometimes in such cases I have obtained benefit from decoction of *simaruba*.<sup>1</sup> In the debilitated condition of these patients *ippecacuanha* is not to be recommended.

Alcoholic stimulants, as a rule, do harm. If circumstances seem to require their use desirable they may be given well diluted, their effects on the system being carefully watched.

It sometimes happens that although the digestive powers are equal to the disposal of 50 or 60 ounces of milk per diem, they are unable to

This drug has for many years been neglected in the treatment of dysentery, at all events by English practitioners. It undoubtedly possesses anti-dysenteric virtues of a high order, and is used very extensively and successfully by irregular practitioners in the East in the various forms of this disease. The official preparation is much too weak and the dose too small.

In the East much larger doses are used. One method of preparing and using it I have seen in vogue is as follows:—*Simaruba*, 2 ounces, divide into four equal parts, put one portion in an earthenware pot in a pint and a half of water for three hours, strain. The patient remain in bed and drink this decoction on an empty stomach every second day for four times. The food must be very plain and consist principally of milk and soft soups. Another method of preparation is to boil an ounce of *simaruba* in twelve ounces of water till reduced to seven drachms, strain ; to this is added one drachm of spirit. This preparation—which is made in an enamelled vessel—a child may take one-fourth and an adult the whole. The dose should be taken every night for four nights.

cope with a larger quantity, a few additional ounces bringing on diarrhoea. In such cases nutrient enemata should for a time supplement feeding by the mouth; indeed, in every case in which the rectum tolerates their presence nutrient enemata may be given with advantage. Sometimes only a very small and utterly inadequate amount of milk can be borne. In some of these cases aerated milk or koumiss agrees better. There is also a class of case in which the power to absorb fluid in any larger quantity is in abeyance; in these, by thickening a small quantity of fresh milk with condensed milk or some form of desiccated milk, or by evaporating in shallow dishes and at a low temperature a portion of the water in fresh milk, the requisite amount of nourishment may be introduced without increasing the bulk of fluid.

Before leaving the subject of the milk treatment of sprue I would repeat that it must be thorough. I have seen cases in which the addition of a biscuit or a rusk, or, worse than these, of bread, interfered with its success, and in which the withdrawal of these "extras" was very speedily followed by solid motions and improved mouth. I would also impress upon my readers the importance of securing a supply of pure milk for these patients. A little lime-water, or bicarbonate of soda, or a pinch of table salt, may be added to the milk with advantage; but such substances as boracic acid—so frequently employed in London by dealers in milk during hot weather—are exceedingly dangerous. I once saw a case nearly lost in this way. If milk is to be the only food no trouble should be spared to see that it is thoroughly good.

If after a thorough trial of milk, say for a fortnight, there is no sign of improvement, what is to be done? As regards feeding, experiment must be made in one direction after another to try whether haply some food or combination of foods can be found which will agree. Peptonised food, malted foods, or some of the many preparations of this description on the market may be tried. Fresh meat-juice, scraped beef, white of egg, pounded chicken, thoroughly cooked arrowroot, corn-starch, decoction of scorched rice, have all been of service; but my experience on the whole has been, that where the milk or milk and fruit treatment has been thoroughly carried out and has failed no other treatment has succeeded.

Dr. Neil Macleod of Shanghai has favoured me with the following note on the treatment of certain cases of sprue:—

It is unquestionably the physician's first duty to resort to milk—milk alone—in dealing with this disease; in nine cases out of ten, if it is not too far advanced, a successful result will be obtained. There are, however, certain cases where with milk, though tried in various forms, the stools continue copious, loose, and offensive, and the patient will insist, and it would appear as if it were the case, that the milk makes matters worse. Flatulent abdominal distension is complained of and discomfort is obvious. In such cases a complete withdrawal of milk and the substitution of fresh beef-juice is well worthy of a trial. The quantity obtained by squeezing one pound of good beef-steak, cleared of fat and underdone, should be given every two hours for seven or eight days.



The addition of salt and a very little pepper renders it more palatable. With the milk, a careful watch of the daily quantity and quality of the stools is absolutely necessary to judge of the effect of treatment. Within forty-eight hours the distension and discomfort will have disappeared. The stools, which are black, will be watery for a time with minute shreds dispersed in them. If improvement continues the shreds will disappear, and, in some cases, the stool may be of the consistence of thin treacle, becoming thicker, till in the second week a porridgy consistency may be reached. If the patient feels hungry and dissatisfied with the juice, a half-slice of toast, thin as thick cardboard, may be given with each dose, in which case the stools will be brown instead of black. The toast should be given only if the patient desires it, and this is usually the case. On this diet, in order to assuage thirst, occasionally a formed stool may occur. At the end of the second week a piece of underdone beef-steak free from fat may be given. It must be well masticated. If the stool keeps its favourable character as to consistence and quantity, a mutton chop without the fat may be substituted a few days; an egg or bread and butter may be added. One portion only should be added, and the result tested by watching the change in the consistence and quantity of the stools. As in the case of the milk, there should be no hesitation in harking back when indications present themselves, the indications being thinning of stools, increase of quantity, and specially indigestion, or any of these. Starchy puddings may next be added, and so far a cup or two of milk daily may now be tried. It must be remembered that meat stools are more offensive than milk ones.

Eventually a combination of the milk and meat treatments succeeds. For example, for five or six days of the week the diet may be exclusively milk, and for one or two days exclusively meat. Meat and milk should be taken at the same meal.

Every effort to check the diarrhoea or to improve the assimilation of food, perhaps it is the wisest course to accept the inevitable, and to adopt a diet and a treatment most in keeping with the wishes and feelings of the patient. We occasionally read of wonderful recoveries on a diet even of coarse fare. It is sometimes possible to continue a diet too long, and it may happen that after a time a certain change in the matter of food will be followed by improvement. Care should be taken to restrict the amount of food. This is most important: the patient's wants should always feel hungry.

Recently Dr. Begg (57), who appears to have seen much of this disease at Hankow, China, says he has found in santonin almost a specific.

He places the patient in bed, and, after a dose of castor oil if necessary, a large enema of warm water, gives five-grain doses of santonin dissolved in a teaspoonful of olive oil every night or twice a day for six times. He insists that the santonin shall be yellow, and that white santonin he has found to be less effectual. The diet, at first milk, is gradually improved as the powers of digestion return.

It is that by this treatment he has cured many cases in which the previous treatment had failed, and also, he says, the yellow santonin treatment has the further advantage of being more permanent in its results.

and occupying a much shorter time. I have tried this method in a considerable number of cases; my experience has not been favourable.

Another system of treatment deserving further investigation is that known as the "fruit cure" or "grape cure." Van der Burg recommends it very strongly. In carrying out this system of treatment the diet must consist entirely of fruit, such fruits being selected as are pulpy and free from coarse seeds, fibres, and excessive acidity. Fresh or tinned apples, pears, peaches, apricots, strawberries, grapes, cucumbers, mulberries, mangoes, liches, lungans, rambutans, melons, gourds, are some of the fruits van der Burg recommends. The juice of oranges and pumelos he permits, but pineapples he interdicts. I have never employed this treatment to the exclusion of milk altogether, but van der Burg, who had a very large experience of sprue in Java, is enthusiastic in its praise, and cites several cases in which it proved highly successful. He says: "I need hardly say that some courage is required to enter on this course, especially when diarrhoea is a prominent symptom; but the good results obtained by others and myself amply justify the treatment."

The subjects of well-marked sprue in the tropics ought to be sent to Europe as soon as possible, and should not return until they have passed at least one hot season in a cool climate, or until their symptoms are thoroughly in abeyance, and they can partake of ordinary food with impunity, and are in a satisfactory state of nutrition.

Before sending the patient on board ship an effort ought to be made to check the more active symptoms; on no account should a patient be sent to endure the miseries of a long sea-voyage when in a dying condition. Before being shipped careful instructions as to diet should be given, and the patient educated in the use of milk; sterilised milk, or at all events preserved milk, can always be procured on board ship, and makes a very fair substitute for the fresh article when this cannot be obtained. Great care must be exercised during bad weather, especially during the extreme heat of the Red Sea, and suitable clothing must be provided and kept in readiness to meet the somewhat sudden transition from tropical heat to the piercing cold of the Mediterranean and Atlantic in winter.

As may readily be imagined, a chronic disease like sprue has been a fruitful field for the quack. His failures, of course, are frequent, but there can be little doubt that many cases of this disease have been cured by what I may call unorthodox methods. Van der Burg mentions a number of drugs and nostrums used in Java by a class of charlatans who profess to be "sprue doctors"; in China, also, there are such people: one, in particular, acquired a great reputation in Shanghai and was extensively patronised. His "cure" consisted in dosing with castor oil or other purgative for several days in succession—perhaps for a week—feeding the patient the while on milk. He then administered an aromatic tincture—possibly of simaruba with opium—along with about a dessert-spoonful of a white powder containing a large proportion of carbonate of lime—possibly cuttle-fish bone or crabs' eyes finely powdered. On alternate days with the tincture and the powder he gave more castor



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## HILL DIARRHŒA

By COL. KENNETH MACLEOD, I.M.S., M.D., LL.D.

**DEFINITION.**—Looseness of the bowels occurring in persons arriving from the plains at elevated places in tropical and subtropical countries. The motions which are passed in the early hours of the day are light in colour, copious, frothy, and liquid or pultaceous. Flatulent dyspepsia, anorexia, and lassitude are essential concomitants. The affection is not alarming or fatal if proper precautions be taken, but is apt to relapse, or become chronic, or to result in an attack of sprue with serious consequences to health and life.

**Etiology.**—This form of tropical diarrhœa, or *Diarrhœa alba*, has attracted most attention in India on account of the migration of Europeans, civil and military, to hill stations during the hot and rainy seasons. The disease was originally described by Grant and others when this custom began, and has excited increased interest as the number of persons proceeding to the hills has grown larger. There is reason to believe that the malady is not confined to India. Hirsch refers to the prevalence of diarrhœa on the Cordilleras of South America, and in the higher regions of Afghanistan and Beluchistan; and doubtless, when we obtain more exact knowledge regarding it, including a clearer definition of the disease, it will be found to prevail in the hills of most tropical and subtropical countries. An elevation of 6000 feet and upwards appears to be necessary to produce hill diarrhœa, but its occurrence at lower levels, as at Hong Kong, has been recorded. Here, again, stricter precision of diagnosis is needed. Hill Indian hill stations are not equally culpable. Those situated on the southern aspects of the Himalayas—Simla, Mussoori, Nynetel, and Darjeeling, for example,—furnish more cases than places such as Ootacamund, Mahableswar, and Abu, which are situated on elevations above the tropical plains. Moore remarks that extra-tropical stations are worse in this respect than intra-tropical. Cases mostly occur in immediate anticipation of the south-western monsoon or during its prevalence. Monsoon influences, which are favourable to the development of cholera on the plains, cause, or aid in causing, this flux on the hills. A high barometer, saturation of the atmosphere with moisture, and a relatively high temperature are the meteorological conditions associated with outbreaks of hill diarrhœa. Cases are usually sporadic and exceptional; but the disease sometimes assumes an epidemic facies, as in that remarkable outbreak at Simla in the year 1880, described by Lambie (2), in which from 50 to 75 per cent of the population suffered, and about 75 per cent of the attacks occurred between the 13th and 15th of June, just before the advent of the rains, when the atmosphere

was saturated with warm moisture. Whole families were simultaneously prostrated, others escaped, and a considerable section of the inhabitants living at a lower level remained exempt. The personal conditions determining attack or exemption have not been clearly defined. The robust and healthy succumb as well as the delicate and sickly. New arrivals are more prone to suffer than permanent residents; men are more liable than women, and Europeans than natives. Children under twelve are seldom or never attacked. The same is true of cholera. Persons who have once suffered are very liable to relapses on revisiting the hills. Acclimatisation occurs in most cases, especially after mild attacks; but some persons are unable to reside in the hills on account of frequent relapses, ending in permanent illness. Insanitation, impure water and milk, chill, fatigue, and excessive eating and drinking have been assigned as causes, but these conditions appear to be rather predisposing or contributory than exciting. The intimate causation of the malady remains to be discovered.

**Pathology.**—The descriptions of hill diarrhœa have been so mixed up with those of other forms of tropical diarrhœa or *Diarrhœa alba* that it is not easy to indicate the pathology of the milder and more transient malady occurring in the circumstances above described. Indeed, Sir J. Fayrer, Moore, and others consider all forms of white flux to be “modifications of the same disease.” Opportunities of performing post-mortem examinations in cases of genuine hill diarrhœa are exceedingly rare. The morbid anatomy of sprue, and of other severer forms of *Diarrhœa alba*, is well known. The intestines are atrophied and degenerated, their absorbent and glandular structures destroyed, the liver and mesenteric glands shrunk, and the body attenuated. In hill diarrhœa the intestinal lesion would seem to be rather catarrhal than atrophic, the small gut being contracted and thickened, and the mucosa swollen and congested (5). No thorough chemical examination of the fæces and urine has been made. Sir J. Fayrer quotes an analysis of the fæces in a typical case of tropical diarrhœa by Dr. Sidney Martin, communicated by Dr. J. F. P. MacConnell. There was an absence of sugar and starch, but an excess of fatty material, and a deficiency of bile which was diminished by more than one half. The bilirubin obtained was unaltered, and only traces of bile-acids were found; the proteids had been converted into albumose. In bad cases the stools are lenteric. As regards the urine the information is still scantier. Moore states that “the urine is frequently natural throughout, sometimes shewing traces of bile.” The symptoms point to an intestinal catarrh, associated with impaired duodenal and intestinal digestion and rapid decomposition of partially digested food. The formation of bilirubin from effete hæmoglobin seems to be in abeyance, and the conversion of the former into stercobilin suspended. The production of bile-acids and salts seems also to be checked. How these disorders of intestine, liver, and perhaps of the pancreas, are brought about it is difficult to say. Crombie (3), who held that hill diarrhœa is a disease *sui generis*, attributes them to altered physical environment, more especi-



ally to a diminished atmospheric pressure, which amounts at Simla to about 3 lbs. to the square inch less than on the plains, and to a high degree of humidity. Hill sickness (vertigo, nausea, and lassitude) appears to be indubitably due to alteration in the physical environment, and it is not a violent assumption that similar circumstances may bring about the hepatic and intestinal disturbances characterising hill diarrhœa. He showed, from the incidents of the Simla outbreak of 1880, which was a typical and very severe example of hill diarrhœa, that neither previous disease or ill health, malaria, insanitary conditions, bad water, contaminated milk, nor scurvy to which the causation of hill diarrhœa has been attributed by various authorities, explained the outbreak. Additional and more searching investigation is needed to elucidate the nature and causation of this remarkable malady.

**Symptoms.** The attack may be ushered in by flatulent dyspepsia, nausea, distaste for food, and lassitude, the stools being solid and clay coloured. This may be the only disturbance of health, and it may pass off in a few days under careful regimen (Crombie), or it may be succeeded by the characteristic looseness. In other cases there is a smart attack of ordinary diarrhœa, followed by white flux. In some instances the symptoms arise insidiously, and present the typical features of the malady from the first. In a fully developed seizure copious loose, frothy, white or drab-coloured motions are passed in the early morning, commonly between 3 and 7 A.M.; after voiding them the patient is relieved. The diarrhœa may be painless or accompanied with colicky sensations due to flatulent distension. During the remainder of the day he feels fairly well, and is able to resume work, but there is always more or less dyspepsia with acid eructations, disinclination for food, and hebetude. These symptoms usually pass off in a few days, but may persist for weeks. In this case anæmia and marasmus with increasing asthenia and lethargy ensue. The abdomen is natural or flaccid, or sunk or distended with gaseous accumulation. The liver and spleen, unless affected by previous disease, are normal in size. There is no pyrexia or jaundice. The tongue is covered with a thick white or yellowish fur. The pulse in severe cases becomes soft and weak. On return to the plains, or descent to a lower level, the symptoms speedily disappear, but they are apt to recur on revisiting the hills. The disease sometimes assumes a chronic form, presenting the characters of sprue (see p. 553). It is seldom fatal in its initial stages, but in its chronic and persistent phases becomes dangerous to health and life.

**Diagnosis.**—The history of the case and a knowledge of the circumstances in which the attack occurred constitute at present the chief means of distinguishing this from other forms of *Diarrhœa alba*. Sprue is a disease of low levels in hot, moist, tropical places. The lingual, buccal, and faucial lesions peculiar to it are absent in hill diarrhœa. The intestinal disorder of sprue is more severe and persistent, and the evidence of intestinal atrophy more pronounced; the shrinking of the liver is very evident, and the anæmia, marasmus, asthenia, mental hebetude and depres-

sion are much greater. Cases of recurrent, inveterate, or persistent white flux consecutive to hill diarrhœa present general and local features indistinguishable from those of sprue. So do cases of *Diarrhœa alba*, appearing *de novo* in temperate climates in persons who have returned from the tropics in broken health. The cases of chronic dysentery described by Twining, in which "patients suffer from a continuance of copious watery purging, sometimes attended with the appearance of fermentation like a mixture of chalk and beer," can hardly present any difficulty in differential diagnosis. It is evident that, for purposes of distinction, reliance must for the present be placed on epidemiological and clinical considerations; the pathological and bacteriological facts are too vague and defective to render any useful assistance.

**Prevention.**—Persons who seem to be specially prone to attacks of this malady should avoid the hills. The journey up should, if possible, be made by slow stages. The greatest care should be taken to avoid chill and fatigue. The abdomen should be kept warm by a cholera-belt or other means, and caution in diet and drink should be observed.

**Treatment.**—Warmth and rest are important indications. Severe cases should be kept in bed, and enjoined to avoid exposure to cold. The diet should be very simple, and if the attack be serious or prolonged a pure milk diet should be resorted to as in sprue (p. 558). The use of peptonised or pancreatised foods is indicated (8). Astringents appear to do more harm than good; opium stops the looseness for a time, but it invariably recurs. Cholagogues have not been of any service. The medicines which have been attended with most success are digestives and intestinal antiseptics. Crombie (3) recommends the use of lactopeptine or of ingluvin given in 12-grain doses about two hours after food. Macpherson advises the administration of perchloride of mercury; Crombie found a teaspoonful of liquor hydrargyri perchloridi, about fifteen minutes after food, serviceable. Salol and naphthol have been employed for the same purpose, namely, to restrain the fermentation of food. If the case does not yield readily to treatment, or shews a tendency to frequent relapses or chronic persistence, a return to the plains or descent to a lower level is absolutely necessary.

KENNETH MACLEOD.

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K. M.

## TROPICAL LIVER

By ANDREW DAVIDSON, M.D., F.R.C.P. ED.

PICAL, formerly known as *Indian*, liver is a disease met with in Europeans who have resided for a long time in tropical countries. In the eighteenth and first quarter of the nineteenth century it was an uncommon thing for a man to spend the whole working part of his life in India without a break. During a period of thirty years or more he had to struggle against the effects of climate, and to run the gauntlet of the numerous maladies peculiar to the tropics, and did not return to his native land until he had completed his official career, or, engaged in mercantile pursuits, after he had acquired a competence or fortune. The retired Indian was readily recognised at the St. Ronan's Balls of that day by his sallow complexion, his imperious manners, and his testy temper, sometimes inclined to melancholy—all of which were ascribed to "liver." The typical Nabob is extinct, and Indian liver in its severer forms is much less common than it was sixty years ago. The shorter period of tropical residence, the more frequent furloughs, the custom of invaliding patients before disease has had time seriously to impair the health, the advance in sanitation which has reduced the prevalence of dysentery and malaria, the greater attention given to outdoor sports, and, above all, the more temperate habits of the present age, have contributed to this result.

*Pathologically*, tropical liver has for its basis chronic congestion of the liver with or without intercurrent acute or subacute attacks of hyperæmia. *Anatomically*, the liver is uniformly enlarged and smooth, of a firm consistency, and bleeds freely on section. In the early stages the enlargement is mainly the result of vascular engorgement, and disappears under free dissection. When it is of long standing there is more or less increase in the connective tissue with atrophy of some of the lobules and hypertrophy of others. The liver sometimes undergoes lardaceous or fatty change. When it terminates in atrophic cirrhosis, as not very infrequently it does, it loses its distinctive characters as "tropical liver." But congestion of the liver cannot exist for any length of time without giving rise to grave disorders—functional and structural—of the gastro-intestinal tract. So close are the anatomical and physiological relations between the liver and alimentary canal that disease of the one is very apt to produce disease of the other, which in turn aggravates the primary malady.

The result of all this is, that in tropical liver the symptoms of impaired function of the stomach, pancreas, and intestinal canal are never absent, and in old-standing cases are sometimes even more obtrusive than those directly referable to the liver. The justification for distinguishing tropical liver as a definite disease rests on the marked differences which exist

between its etiology, symptomatology, and associated pathology and those of congestive liver diseases in temperate climates.

**Etiology.**—The more important causes of tropical liver are:—(1) A high temperature and chill; (2) Dietetic errors, quantitative and qualitative, aggravated by the inactive life to which tropical conditions dispose the European resident; (3) Malaria; (4) Dysentery and diarrhoea.

**Heat.**—Tropical liver is essentially a disease of the native of a temperate or cold climate residing in the tropics. It is a part of the white man's burden. This points to the predominating influence in its causation of a hot climate on constitutions not adapted to it. Indeed, even in temperate climates the initial stage of hyperæmia is occasionally observed as a consequence of an unusually long-continued heat-wave. As the cause of these attacks is only temporary, so the effects are transitory. In the tropics, on the other hand, the cause is continuous in its operation and its effects are more permanent. But the influence of heat on the European in the tropics depends not only on its degree and duration, but also on the constitution, and still more on the habits, of the individual. Some persons experience a constitutional difficulty in keeping the temperature of the body normal. The slightest exertion raises their temperature or sends them into a profuse and weakening perspiration, and the least irregularity in diet manifests itself in disturbance of the functions of the liver. Although it is largely the case that every one has the sort of liver in the tropics that he deserves, this is not absolutely true, for some with the greatest care cannot avoid congestion of the liver and its consequences. Others have a more efficient heat-regulating apparatus, and more readily become adapted to tropical conditions. It is outside the scope of this article to discuss the manner in which heat produces liver disease. The doctrine that the lessened functional activity of the lung throws work upon the liver which in temperate climates falls to the share of the lung to perform rests on no solid basis. There is, in fact, no evidence that the consumption of oxygen in respiration is materially diminished in the tropics. That the liver has more work to perform, and that this additional work is mainly responsible for its breakdown, is a truth, the recognition of which is essential to a clear conception of the pathology of tropical diseases of the liver. This additional work, however, arises from the side of the gastro-intestinal canal, not from that of the lung. An obvious way in which heat disposes to hepatic disease in general, and to tropical liver in particular, is the liability it induces to chill from its depressing influence on the vasomotor system. One of the most common exciting causes of active hyperæmia of the liver and hepatitis is a chill after profuse perspiration, or exhaustion from exposure to sun and fatigue. A draught of cool air at night, a cold bath taken inopportunistically, or a wetting after being overheated is sufficient to set up mischief in a torpid liver. The influence of cold and chill in causing attacks of congestion is well exemplified in the case of those who return to England after long years in the tropics. The system in time becomes, to a certain extent, set to heat, and a process of reacclimatisation has to be

through. Dr. J. Anderson has pointed out very justly that the tropical resident "changes back to the conditions of his early life with much more difficulty, inasmuch as he is constitutionally less elastic, less adaptable to the second change than to the first. The habits of an life have become natural to him, and we have to add to the loss through the pathological changes met with as the sequelæ of tropical diseases." The impression of cold on the vasomotor system readily gives in the old Indian to what is called "a chill on the liver." We may regard heat in its direct and indirect effects on digestion, metabolism, and the nervous system of the European as the most potent factor in the causation of tropical liver.

*Excess of food*, particularly of animal food, obviously increases the work of the liver, and gives rise to hyperæmia. When the food is not in excess, but of an indigestible or irritating kind, such as rich dishes, hot curries, and strong coffee, the evil is greater, as they disturb the functions of the stomach and liver. Weakened digestion is one of the early effects of tropical heat upon the constitution of the European. When the stomach is overtaxed by imprudences in diet, gastric digestion is imperfectly performed and the toxic products of abnormal fermentations, absorbed from the bowel, irritate the liver. Alcohol, except in the strictest moderation, is a hepatic poison. In warm climates it cannot be indulged in freely for any length of time without impairing the integrity of the liver. Excessive smoking, although vastly less injurious, has likewise a detrimental influence on the stomach and liver. Dietetic errors of the kind we have mentioned are all the more harmful that the high temperature indisposes to muscular exercise. It is a matter of experience that those who take active exercise in the cool of the mornings and evenings are less liable to liver disease than those who lead an inactive, sedentary life. Däubler has pointed out that the European infantry regiments in the East enjoy better health than the rest of the troops, and are also more resistant to disease. Their duties ensure them regular exercise in the open without undue fatigue and without raising the body-temperature to a degree incompatible with health. Walking and riding are the best kinds of exercise for the average European in the tropics. Athletic games are unsuited to the old resident, but in the morning they may be practised with great advantage to the health, in the cool of the evening, if care be taken to change the clothes immediately after the game is finished. But while all this is true, it may be laid down as an axiom, that no amount of exercise will obviate, in the long-run, the consequences of indulgence in the pleasures of the table.

*Malaria* is a common, and, according to some, the principal cause of tropical liver, but it is doubtful if it gives rise to serious and permanent liver disease so frequently as is supposed, apart from the action of heat and other predisposing and co-operating factors. In temperate climates malaria is seldom followed by liver disease, except in alcoholics. In the tropics congestion of the liver and hepatitis, as a consequence of malaria, are comparatively rare among the natives, who are nevertheless

more subject to malarial infection than the European. This will be seen from the following figures shewing the incidence of malarial fever, congestion of the liver and hepatitis in the European and native troops respectively for the year 1901

	European Army	Native Army
Malarial fever . . . . .	299.5	372.7
Congestion of the liver and hepatitis	16.2	10.7

The only explanation I have to offer of these figures is that, although the virus is the same in both cases, the livers on which it acts are different. The combined effects of heat, alcohol, and dietetic errors on the liver of the European render it seventeenfold more liable than that of the native to this class of diseases in spite of the greater liability of the latter to malaria. The result of frequent attacks of malaria, in the European, is in many cases to lay the foundation of chronic enlargement. The effects of the infection on the system, too, may persist long after the parasites have disappeared from the peripheral blood. It is no uncommon thing for old malarials to suffer for years after they return home from tropical attacks, neuralgias, and congestions of the liver. Chevers states that he experienced more severe paroxysms of intermittent fever in Bayswater for five or six years after his return from India than he ever had at Chittagong, where he contracted the disease. Ronald Martin was "persecuted," as he says, every spring for thirty years after leaving India by a fever contracted when a young officer. Whatever may be the nature of these attacks, and malaria can scarcely be excluded from the etiology, they often aggravate the symptoms of tropical liver.

*Diarrhoea and dysentery*, when chronic, play an important part in the pathogenesis of tropical liver and abscess. Ewald remarks that "the liver forms a sort of catch pit between the right side of the heart and the blood of the portal vein, which receives all the toxic matter absorbed from the bowel and either holds it and gives it up little by little to the blood, or destroys it, or excretes it again with the bile into the intestine. In chronic dysentery and diarrhoea the amount of toxic matter is increased, and the capacity of the liver to deal with them will depend on its integrity and on the amount and quality of the substances absorbed. The factor of primary importance as regards the effects of dysentery in giving rise to disease of the organ is the integrity of the liver itself. This is proved by the rule that while the native of India suffers more than the European from dysentery and diarrhoea in the ratio of 5:35, he is seventeen times less liable to congestion of the liver and hepatitis, and from twenty to twenty five times less liable to abscess. In other words, he suffers less than the European from all kinds of liver disease, and less still from the graver forms. The reason of this is that in the native the liver is functionally adequate to render innocuous the poisonous substances absorbed from the bowel, which otherwise would give rise to hepatitis and impair its resistance to the bacterial and amoebic infections and toxins associated with dysentery and diarrhoea.



**olution of Tropical Liver.**—The liver possesses a remarkable power of dilatation by vascular repletion. During a paroxysm of ague the enlargement may sometimes be traced by percussion at short intervals, when the fit is over it will be seen to diminish in size with nearly equal rapidity. In health the quantity of blood contained in the liver is constantly undergoing fluctuations, according to its functional requirements.

During digestion an augmented supply of arterial blood is sent to the stomach, liver, spleen, pancreas, and intestines, with a corresponding increase in the amount conveyed to the liver by the portal vein.

This physiological hyperæmia is in relation to the increased secretion of bile poured into the duodenum when gastric digestion is completed.

The first departure from strictly physiological hyperæmia arises from any cause, the amount of blood sent to the liver is in excess of its functional requirements, resulting in a secretion of bile beyond what is necessary for healthy digestion. This, which may be called *irritative hyperæmia*, is the kind of congestion to which newcomers in the tropics are liable. Not that all are attacked in this way, or in the same manner.

Copious bile-coloured stools usually ensue, relieve the vascular congestion, and prevent for a time any serious disturbance of the general system.

If care be taken at this stage to reduce the intake of food, and to regulate the habits in other respects in accordance with the requirements of tropical life, this irritative hyperæmia will subside without harm to the liver.

If the conditions giving rise to it persist, a state of torpor of the liver sooner or later sets in. This is generally represented as simply a state of functional exhaustion consequent on the long-continued excess of activity. It is something more. We have no definite demonstrations of the state of the liver in this initial stage, but we can hardly be wrong in ascribing the hyperæmia to the irritation resulting from the additional work thrown on the organ by increased metabolism, the kind as well as the amount of work may here be a matter of importance.

So long as the liver is able to transform the material sent to it, an increased secretion of bile is the only evidence of the stress to which it is subjected. When the work exceeds the capacity of the liver, the secreting cells probably become infiltrated with imperfectly formed substances, and their bile-forming function is impaired.

Swollen hepatic cells pressing on the bile canaliculi will offer an obstacle to the free flow of the secretion. Vecchi's experiments seem to prove that an obstruction to the flow of the bile weakens the physiological resistance of the liver to such an extent that suppurative hepatitis is produced by the introduction into the liver, by the vena porta, of pathogenetic germs that failed to provoke a reaction so long as the flow of bile was not interfered with. Although we have here to do with a toxic rather than an infective process, the free flow of bile is doubtless one of the conditions determining the health of tropical liver. Howsoever caused, this state of torpor, following irritative hyperæmia, is the first stage in the evolution of the

disease. The symptoms of this condition are want of appetite, at first most marked in the morning; a coated state of the tongue, a bitter or saltish taste in the mouth, and a feeling of weight or fulness in the hypochondrium and epigastrium, which are often tender on pressure. When of some standing the liver will be found enlarged. Digestion is slow and painful, with heartburn and flatulence. Constipation is often obstinate, and the stools pale and pasty. But attacks of diarrhoea occur from time to time, the stools being pale and frothy, or dark and watery, and sometimes mixed with mucus. Hemorrhoids are of frequent occurrence. The patient is drowsy after meals, but often sleepless at night, complains of headache, is disinclined to muscular exercise, incapable of sustained mental effort, and is frequently depressed.

By prudence in diet, avoidance of alcohol, and careful habits of life, recovery generally takes place, and the liver regains its normal activity; but if the torpid condition persist, the patient stands under the imminence of serious hepatic disease. An excess at table, a chill, an attack of malaria or dysentery may at any time precipitate acute congestion, hepatitis, or abscess. Acute congestion is the most common accident supervening on liver torpor, and leads, if repeated, to chronic congestion and enlargement. There are pain, weight, and oppression in the right hypochondrium; enlargement and tenderness of the liver with more or less fever; pain on deep inspiration or evoked by a sudden jolt, pain or aching in the right shoulder radiating down the arm or seated in the region of the scapula; tenderness in the epigastrium with nausea or vomiting. The bowels are constipated and the stools pale, or they may be loose and frequent, and passed with gurgling and flatulence. If the fever rise above 102° F the disease is spoken of as hepatitis. A *torpid congestion* and *hepatitis* are different grades of the same disease. When the attack has been set up by a chill, severe diarrhoea is common, and may persist for weeks. When malaria has given rise to the congestion, the spleen is often considerably enlarged; and in the *intermittent anasarca* of the lower extremities is frequently present.

But the evolution of tropical liver is, in many cases, much more insidious. A chill, over fatigue, exposure to the sun, or some irregularity in diet gives rise to slight but oft-recurring uneasiness or tenderness in the liver, with anorexia and indigestion. The symptoms may not be so severe as to confine the patient to bed or house. After a time, however, the liver is found to be hypertrophied, and the spleen perhaps slightly enlarged, or more decidedly so if the patient have suffered from malaria.

**Symptoms.**—The symptoms of tropical liver vary extremely according to the stage, severity, the frequency of exacerbations, the presence or absence of malaria, and the extent to which the digestive system is involved. In its mild form they are those of torpid liver. In its higher grades there is an appreciable enlargement of the organ in all directions—sometimes slight, but in other cases the liver extends for two or three inches below the costal margin, occasionally it reaches the umbilicus. Acute pain is not much complained of, but the patient generally knows he has a liver

imes there is a dull, dragging weight or soreness in the right hypochondrium, with aching in the shoulder and down by the scapula. The appetite is poor, digestion slow, sometimes painful, with flatulence. There may be acidity and heartburn from imperfect digestion of carbohydrates, or eructations of foul-smelling gases from putrefactive changes in the proteid elements of food, with frontal headache and troubled nights. The urine is at one time limpid, abundant, and passed frequently; at another time high-coloured, scanty, and loaded with mucus. Tourtoulis has insisted on diminution of urea as a feature in the cases of tropical liver. The bowels are habitually constipated, and the countenances paler than normal, but an acute attack of indigestion may be followed by a troublesome diarrhoea. The spleen, apart from malarial congestion, is only slightly enlarged, but in malarial subjects it may attain considerable dimensions.

The complexion is pale and sallow, sometimes of a faint lemon tinge. Rarely is there any undoubted jaundice, and this if present is transitory. When the disease is advanced or severe, the patient is anemic, weak, and more or less emaciated. It not infrequently happens after a number of years of tropical residence the patient becomes liable than at the beginning of his career to exacerbations of acute or subacute congestion, but these recur when he returns home. The chronic symptoms in these circumstances frequently become aggravated, and may be accompanied with irritability of temper and fits of despondency.

After a year or two at home an improvement sometimes takes place, and with prudence, which can never safely be dispensed with, the patient may enjoy fair health. In other cases gastric troubles and malaria gradually undermine the health; or portal cirrhosis may set in and lead to a fatal issue.

**Treatment.**—Tropical liver is not an inevitable consequence of tropical residence. It is to a large extent, at least in its more severe forms, a preventable disease. But the European cannot take the same precautions with his liver in the tropics that he does at home. By a careful moderation of the amount of food taken to the weakened powers of digestion; by a restricted use of animal food; by the avoidance of indigestible and highly seasoned articles of diet, and the strictest abstinence in, or, what in most instances is better, by an entire abstinence from alcohol; by regular active exercise, short of exhaustion, and at suitable hours; by the avoidance of unnecessary exposure to sun and chills; by adopting a rational dress, and by carefully regulating the action of the bowels, the European may live for years in the tropics without suffering serious inconvenience from the liver, if he be fortunate enough to escape malaria and dysentery.

In the initial stage of liver torpor, when there is little or no enlargement, the indications are to insure regular action of the bowels and to impart tone to the congested stomach. A pill of podophyllin, combined with aloes and ipecacuanha, in doses sufficient to obtain one or two free stools daily, is to be given, and the digestion assisted by 10 to 20

minims of dilute nitro-hydrochloric acid and 10 minims of the tincture of nux vomica in gentian or quassia. When a laxative for more constant use is necessary, the liquid extract of cascara with euonymin generally answers well. When there is a feeling of weight or discomfort in the right hypochondrium, with or without evident enlargement, more active treatment should be resorted to. Sulphate of sodium, or artificial Carlsbad salts consisting of two parts of sodium sulphate to one each of sodium chloride and bicarbonate, should be given in a purgative dose in the morning; or in smaller doses more frequently, with an occasional dose of 5 to 8 grains of calomel or blue pill at night. This treatment should be continued for two or three weeks till the symptoms disappear.

When active congestion or inflammation is set up from a chill or other cause, with enlargement, pain, and tenderness of the liver, the patient should be confined to bed and put upon a milk diet. Salines in repeated small doses should be given, and, when the case is severe, leeches may be applied to the anus, and turpentine stupes over the region of the liver. Chloride of ammonium in doses of 15 to 20 grains should be administered four times a day. When the hepatic congestion is accompanied with diarrhoea, as not unfrequently happens, one or two doses of 20 to 30 grains of ipecacuanha should be given, and no premature attempt made to arrest the diarrhoea.

In the congestion and enlargement of the liver and spleen with anæmia consequent on malaria, a combination of the sulphates of magnesium, quinine, and iron, with dilute sulphuric acid, often proves very useful. In the extremely malarious year, 1879, in Mauritius, when enlargements of this kind were very common and often complicated with anasarca, the use of the four sulphates—as the mixture was called—was generally followed by a marked reduction in the size of the liver and spleen, and disappearance of the anasarca within a week or ten days. When the urine was scanty and the heart's action feeble, small doses of digitalis were given. It is in chronic congestions, especially those of malarial origin, that marked benefit is derived from local packs of nitro-hydrochloric acid over the liver. Eight ounces of dilute nitro-hydrochloric acid are added to a gallon of water at a temperature of 98° F., and cloths soaked in this mixture are applied to the whole region of the liver and the upper part of the abdomen, and changed frequently; or the acid may be applied by means of spongiopiline, the application being intermitted when it causes too much irritation of the skin.

In obstinate enlargements of the liver a change to a temperate climate is advisable, the utmost precautions against chill being inculcated. A course of the waters of Carlsbad, Kissingen, Friedrichshall, or Vichy often proves advantageous in these cases. Of our home spas, Harrogate is the only one that requires mention.

Anæmia and dyspepsia are frequently prominent symptoms in those who have returned to England after many years in the tropics. The anæmia may be the result of previous malarial infection aggravated by recurrences of congestion. In these cases quinine in combination with

iron is indicated; and, as a matter of experience, quinine in small doses is often serviceable in the tropical liver of those who have suffered much from fever, even when there are no special symptoms to indicate its use. The anæmia, in other cases, is rather to be ascribed to inveterate dyspepsia resulting from the liver disease with defective secretion of gastric juice and atony of the muscular coat. When the dyspepsia is not the result of advanced chronic gastritis an improvement in the circulation of the liver may be expected to result in an amelioration of the stomach symptoms. The digestion is to be assisted by the administration of pepsin, hydrochloric acid, and nux vomica. If there be much flatulence and constipation, ox bile, given in the form of pill and coated with keratin, is of service. Iron and tonics will also be useful if free action of the bowels is maintained.

The sufferer from tropical liver and dyspepsia is frequently a victim to mental depression, caused partly by disease and partly by no longer having any duties to occupy his mind. Foreign travel may be recommended with advantage in these cases; the frequent change of scene and company diverts the patient's attention from his morbid sensations, while the enforced activity in the open air promotes the circulation and improves the appetite. When tropical liver terminates in cirrhosis the treatment is that proper to this disease.

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A. D.

### TROPICAL ABSCESS OF THE LIVER

By ANDREW DAVIDSON, M.D., F.R.C.P. Ed.

UNDER the term "tropical abscess of the liver" are included the single or multiple large abscesses, whether dysenteric or idiopathic, which form such a characteristic feature in the pathology of warm climates. Pyæmic abscesses and suppurative cholangitis, which are not peculiar to any climate, will be dealt with separately in Vol. IV.

On few subjects that have received equal attention are opinions more discordant than on the pathogenesis of tropical abscess. Is there an idiopathic variety, or are all tropical abscesses of dysenteric origin?

<sup>1</sup> The word "idiopathic" is not free from objections, as pointed out in an editorial footnote at p. 164, vol. IV, 1897. It is here used for the sake of convenience, and "in its negative bearings" in the sense of non-dysenteric.



When associated with dysentery, does the intestinal ulceration precede and give rise to the hepatic inflammation, or are the two affections the result of a common cause acting simultaneously, successively, or alternately on intestine and liver? Is liver abscess a complication of amœbic dysentery only, or does it also arise in connexion with the bacterial form? When associated with amœbic dysentery, do the amœbæ act merely as carriers of pyogenetic organisms, or do they co-operate with these in giving rise to suppuration, or are they the sole agents in its causation? We shall endeavour to review the data, such as they are, bearing on these points as fully as our limits permit.

**Etiology.** — *Geographical Distribution.* — The large hepatic abscess, except as a result of injury, is, as Hirsch remarks, one of the rarest diseases of temperate and cold climates. Graves relates a case of apparently idiopathic abscess of large size in a glass-blower, a trade in which the workmen are subjected to great heat. The cases of indigenous origin met with in our own country are almost invariably a sequel of diarrhoea or dysentery. Hepatic abscess as a complication of dysentery was more frequent in Ireland in the first quarter of the nineteenth century than at the present day. Cheyne met with four cases of liver abscess in thirty autopsies for dysentery in Dublin during the epidemic of 1818, and two of these were large abscesses. In a return of the causes of death in the army serving in Ireland, from the 1st January 1818 to 1st October 1826, twenty-four deaths from liver abscess are recorded. Instances of this kind are extremely rare. Dr. Gemmel found abscess of the liver twice in eighty fatal cases of colitis at the Lancaster Asylum. Other cases are to be found scattered in medical literature; but it may be safely asserted that liver abscess, as an indigenous disease in the United Kingdom, at the present day, is a pathological curiosity. The same holds good for France, Germany, and northern and central Europe generally; even the amœbic form of dysentery, occasionally met with in these countries, is rarely followed by abscess. We have definite accounts of its more frequent occurrence in some parts of Rumania, Italy, and Dalmatia. In Gibraltar it gave rise to a death-rate of 0·11, and in Malta to one of 0·43 per 1000 during the four years 1888-91, as compared with a ratio of 1·35 for Bengal; but it is not certain whether the disease was, in every instance, contracted at these stations. In Cyprus, judging from the Colonial reports, hepatic abscess must be rare among the natives, as in 1903 no case occurred out of nearly 20,000 patients treated, of which number 261 were suffering from dysentery. Respecting Greece, Turkey, and Asia Minor, all we can say is that liver abscess is met with in these countries more frequently than in Europe, but to what extent is uncertain.

India provides the most trustworthy statistics of hepatic abscess, and the following figures refer to its incidence in the European and native troops and in the prison population:—



	European Army. 1891-1900.	Native Army. 1891-1900	Jail Population. 1901-1903.
Death-rates per 1000 from liver abscess in India	1.25	0.06	0.09

It will be seen from this table that the death-rate is twenty-one per cent higher among the European than the native troops, and fourteen per cent higher than among the prisoners. The prevalence of the disease varies greatly in different regions of India, as is evident from the following table, which gives the death-rates per 1000 from liver abscess in the European army for 1901-3 in the different geographical areas into which the country is divided. For the sake of comparison, the death-rates from dysentery for the corresponding years and areas are added :—

	Liver Abscess.	Dysentery.
Malabar Coast, Bay Islands	2.30	3.70
Malabar Inland	1.35	0.00
Madras, Orissa	6.55	3.30
Deccan, Deccan Plateau, Chota Nagpur	2.34	0.93
North-West Frontier, Sub-Himalaya	0.98	1.07
North-West Frontier, Indus Valley, N.W. Rajputana	0.38	0.22
Rajputana, Central India, Gujarat	1.75	1.17
Bombay	1.27	0.26
Malabar Coast	1.06	0.21
North India	1.10	0.19
Stations	1.08	0.66

A glance at the above table shews that the death-rates from liver abscess and dysentery bear, upon the whole, a direct relation to one another, yet not so close and constant as to give support to Chauffard's opinion that "the more frequent, grave, and persistent dysentery is in a country, in the like proportion will suppurative hepatitis be frequent, grave, and persistent."

Liver abscess is comparatively rare among the natives of Ceylon, and in 1903 all the hospitals, asylums, and public institutions furnished 34 admissions and 16 deaths, while dysentery, chiefly bacterial, gave 2294 admissions and 658 deaths.

Liver abscess appears to be less common in the Malay Peninsula than in India. There were no deaths among the European troops in the Straits Settlements during the four years 1888-91. Nor does it seem to be at all frequent among the native population. In the year 1893 there were only five admissions for liver abscess in the hospitals of the Straits Settlements serving a population of 572,449. During military expeditions in the Malay Peninsula, however, dysentery and liver abscess come more into evidence. Thus, Conwell observed no fewer than seventeen cases of liver abscess in the General Hospital of Penang during the two months of June and July 1827. In Cochin China and Tonkin liver abscess

forms from 2 to 3 per cent of the total deaths among the French soldiers.

The experience of the American army proves the prevalence of liver abscess among strangers in the Philippine Islands. Strong found liver abscess in fourteen out of ninety-seven autopsies of amoebic dysentery. Considering its prevalence in the Philippines, Java, and Sumatra, it is all the more remarkable that there is so little liver abscess in South China. Respecting Hong Kong, the hospital returns for 1904 state that, "though dysentery is common enough here, liver abscess is comparatively rare, more especially among the Indians, who, however, suffer badly from dysentery." This statement is justified by the returns of the hospitals for that year, which shew no case of liver abscess among the 2607 patients treated. The disease appears to be rare in Japan, where the dysentery is almost entirely of the bacterial kind.

Turning to Africa, liver abscess is common among the European residents in Egypt in connexion with amoebic dysentery. The ratio of admissions among the British troops for the ten years 1895-1904 was 10 per 1000. The natives, on the other hand, suffer little from the disease. Griesinger met with two cases only of abscess in 186 autopsies for primary dysentery in the native hospital. The French suffered much from liver abscess in Algeria in the early years of their occupation when military expeditions were frequent, but of late years it has become much less common. In the hospitals of Philippeville and Bougie liver abscess formed from 12.4 to 9.6 per 1000 of the total deaths during the ten years 1867-76. In Senegal liver abscess has always been one of the most fatal diseases of the Europeans, but it is comparatively rare among the natives. It appears to have become much less common in Sierra Leone in recent years, if accounts of its former prevalence in that colony are to be credited. Of twenty-nine deaths of Europeans registered in 1900-1, none was from liver abscess, and only one case occurred in the native hospitals in the same years out of 2551 admissions. Earlier reports speak of liver abscess as severely endemic along the whole of the north-west coast of Africa, but this does not appear to represent the state of things at the present day. Macfarlane states that he has never seen a case of liver abscess at Lagos, although dysentery is prevalent. From the Equator southward the disease is not at all frequent, with the exception of some parts of the Congo Free State, where Dryepondt reports it to be rather common as a complication of dysentery. Liver abscess was extremely rare as a sequel of dysentery (which was almost entirely bacterial) in the late war in South Africa (29). In the non-malarious island of St. Helena hepatitis, according to Lombard, causes 29 per 1000 of the total deaths. Few details are available respecting its prevalence on the east coast of Africa; but as regards Zanzibar, we have the express testimony of Irigo to the effect that hepatitis and abscess of the liver are almost unknown there. It is very different in Mauritius, where the disease is known to have existed since the first settlement of the island, and long before the advent of malaria. In 1904 thirty cases were treated in the hospitals

but this in no wise represents its actual frequency, as the white population, which suffer most, do not, as a rule, enter the hospitals.

Abscess of the liver is rare in the northern states of the United States, but Prof. Osler informs us that it is more frequent in the south. Accounts by Sullivan point to its rather frequent occurrence in New Orleans.

It has often been noted with surprise that liver abscess should be so rare in the West Indian Islands as compared to the East Indies, but this is undoubtedly the case. The death-rate of the troops stationed there for the four years 1888-91 was 0·23 per 1000, as compared with 1·35 for Bengal. Earlier and later observers agree in representing liver abscess as rare in Jamaica. I have before me a statement of patients admitted into the Kingston Hospital (9) from the 1st November 1807 to the 31st October 1808. The total admissions numbered 845, of which 268 died, including 17 from dysentery, but none from liver abscess. Dr. D. M. Ross states that he has never seen a case following dysentery contracted in the island. In Trinidad there were only four admissions for liver abscess in 1904-5 out of 14,102 treated. In the Leeward Islands generally, the disease appears to be very rare, judging from the Colonial Hospital Reports. It is undoubtedly more common in Cuba, according to Sullivan's accounts; and here it is generally, but not exclusively, a complication of dysentery. We know that it is not infrequently met with among the French soldiers stationed in Martinique and Guadeloupe, but exact figures as to its prevalence are wanting. Liver abscess is rare in British Guiana, where there were only 11 admissions for the disease out of a total of 14,822 from all causes in 1903-4. There is reason to believe that it is equally rare in Surinam and Cayenne. In some parts of Brazil liver abscess is rather frequent, especially among sailors and strangers. Nowhere on the western continent, or perhaps in the world, is liver abscess so fatal as along the northern coast of Chile and the coast of Peru. About 21 per cent of the autopsies at Valparaiso in 1871 revealed abscess of the liver. The disease ceases to be endemic in the more temperate districts of Chile, south of the 35th degree of latitude.

From a survey of its distribution we may conclude (a) that the large liver abscess is practically restricted to tropical and subtropical countries; (b) that its prevalence is not strictly regulated by latitude or mean temperature—some moist and hot countries, such as British Guiana, being comparatively exempt; (c) that it is met with in non-malarious countries, but this does not exclude the influence of malaria as a disposing cause of abscess; (d) that it is not equally distributed over a region where it is endemic,—there are stations, such as Barrackpur, 15 miles above Calcutta, that are hotbeds of liver abscess; (e) that liver abscess is most common in countries where amœbic dysentery prevails; (f) that the natives of a country where it is endemic are much less liable to liver abscess than strangers coming from cold latitudes, although it has not been proved that they are less subject to amœbic dysentery.

*Altitude.*—The influence of altitudes sufficient to reduce the mean

summer temperature to that of temperate regions in diminishing the prevalence of liver abscess is incontestable. Rouis states that in Algeria the disease is rare or unknown at elevations of 3000 mètres; and Jourdain and Tschudi both point out the rarity or absence of liver abscess at high elevations in Mexico and Peru. At the same time, it is often observed to be more frequent at moderate elevations than at the sea level, where local insanitary conditions favour the prevalence of dysentery. At Secunderabad, for example, 1700 feet above the sea level, extremely fatal dysentery, often complicated with liver abscess, decimated the troops year after year before the demolition of the old infantry barracks and the introduction of much-needed sanitary improvements. The following table gives the admissions per 1000 for liver abscess in the European army of India at various elevations for the three years 1895-97. It testifies at once to the influence of altitude and of local conditions on the prevalence of the disease.

Below 100 feet.	100-500.	500-1500	1500-3500.	3500-5000.	5000-8000	8000-12,000
2.8	2.4	1.7	2.1	1.9	1.2	0.0

*Meteorological Conditions.—High Mean Temperature.*—The influence of a high mean temperature in determining the prevalence of liver abscess may be inferred from its latitudinal and altitudinal relations. Rouis observed that the years in which the temperature in Algeria was unusually high, such as 1843, 1847, 1849, and 1853, were those which invariably furnished an excessive number of cases of liver abscess. The way in which a high temperature favours the evolution of the disease is not so evident. Heat, no doubt, disposes the body to hepatic inflammation, but it may also act by favouring the multiplication of amœbæ in external media, thus increasing the prevalence of intestinal amœbiasis, which is one of the commonest causes of hepatic abscess. In numerous individual instances prolonged exposure to extreme tropical heat has appeared to be the determining cause of abscess, but in these cases co-operating factors cannot be excluded.

*Vicissitudes of Temperature.*—Attention has already been directed to the comparative rarity of liver abscess in countries, such as the Straits Settlements and British Guiana, with a hot, moist, but equable climate, as compared with Senegal and Chile, where the range of temperature is high and the fluctuations sudden. We shall be the less disposed to question the influence of vicissitudes of temperature as a factor in determining the varying prevalence of the disease in different tropical regions if we bear in mind the frequency with which abscess develops in those who return to Europe from the tropics in winter or early spring. Some of these cases would probably not have terminated in abscess had the patients not been subjected to the inclemency of an English winter. Vicissitudes of temperature will certainly not suffice to give rise to an abscess in a healthy liver; but the case is different when the organ is diseased by tropical residence and chronic dysentery. Maclean remarked that in his experience the most frequent cause of acute congestion of the liver

sudden change of temperature. "I call to mind," he says, "examples not only of acute congestion of the liver brought on in this way, but of fatal suppurative inflammation." He relates an abscess developing in India, as the result of a chill, in a young man who does not appear to have suffered from dysentery. A case of this kind came under my observation in Mauritius, the subject of which was a young Hindoo of intemperate habits, had never suffered, so far as I could make out, from dysentery. His account was that after a long journey on foot his way home, lay down on the damp ground, and fell asleep. On waking next morning he felt severe pain in the right hypochondrium, followed by fever, and terminating in abscess. In this case the relation between the chill and the abscess can scarcely be

*Prevalence.*—According to most of the Indian authorities, abscess is most common at the end of the rains and the beginning of the dry season, when the range of temperature is greatest. Major Macgregor, from an analysis of the dates of 236 admissions in Calcutta, there is no season of special prevalence of the disease. At Senegal, on the other hand, where the distinction of seasons is more marked, Thevenot found the admissions in 51 cases to be distributed as follows:—October to March 31, April to June 11, July to September 9, shewing a distinct preponderance of cases in the cold season. In the tropics the diurnal ranges are extreme. This represents, I believe, the prevalence of hepatic abscess wherever similar conditions

*to Dysentery.*—Olmédec's definition, "*l'hépatite c'est la dysentérie du foie*," expresses epigrammatically the close relation which has been recognised between dysentery and inflammation of the liver. Modern pathologists at the present day, excluding all other agents, regard dysentery as practically the sole determining factor in the production of the tropical liver abscess. Vaillard, one of the most recent authorities on the subject, says, "*Peu nombreux sont les abcès du foie dans les pays chauds, si même ils existent réellement.*" Liver abscess, it is said, is not an abscess like all other abscesses in the character of its pus, which points to it as the product of a specific organism. Liver abscess is tropical dysentery; and its prevalence in a country or locality is determined by the prevalence and intensity of dysentery in such a country or locality. This is attractive from its simplicity, and also from the large amount of evidence it contains. Whether there is only one form of tropical abscess, exclusively of amœbic origin, is the point we have now to

ascertain. Abscess is foreign to the pathology of the epidemic dysentery of temperate climates. Finger did not meet with a single case of liver abscess in 11 dysentery autopsies in Prague from 1846 to 1848, and found only one abscess in 279 fatal cases of dysentery in the same city from 1880 to 1884. The same is true of the epidemic

dysentery of the tropics. The dysentery of war in temperate climates is rarely followed by abscess. Marston observed two cases only of liver abscess among the numerous soldiers from the Crimea suffering from dysentery who came under his care in Malta. The same absence of liver abscess in connexion with dysentery was noticed by Burkardt during the Franco-German war; and, as we have seen, liver abscess was extremely rare in the dysentery of South Africa during the Boer war. Multiple liver suppurations, containing the *Staphylococcus pyogenes aureus* only, were, however, found by Birt in one-half of the cases of dysentery due to Shiga's bacillus, in which superficial gangrene was present and large excavated ulcers were formed. Equally remarkable is its entire absence in some of the most fatal outbreaks of institutional or asylum dysentery in temperate climates. Baly did not meet with a single case in the many hundreds who died of dysentery at Millbank. Nor is it much more common in the prison dysentery of India, occurring, according to Major Buchanan's figures, in 1 out of 681 cases. As it is now ascertained that epidemic and institutional dysentery, and that of war in temperate climates, are of the bacterial type, we are warranted in concluding that bacterial dysentery is not usually associated with large liver abscess.

One form of dysentery, which we now recognise as amœbic and as practically restricted to the tropics, is proved, on the other hand, to be frequently complicated with or followed by liver abscess. In attempting to establish the frequency of this complication, the statistics of earlier observers, who were ignorant of the distinction between the two forms of dysentery, are of no use. Hence, we are confined to the scanty observations of recent years. Kruse and Pasquale found liver abscess in 4 out of 11, Councilman and Lafleur in 6 out of 9, and Strong in 14 out of 96 autopsies of amœbic dysentery. These figures give an average of one case of liver abscess in four or five fatal cases of amœbic dysentery. The proportion will, of course, be considerably less if cases which recover as well as those which die are taken into account. Harris met with liver abscess twice in thirty-five cases of amœbic dysentery which he investigated. The frequency with which the hepatic complication occurs varies, no doubt, in different countries, seasons, and circumstances, and also in different races. We can hardly be wrong in thinking that amœbic dysentery is less frequently followed by liver abscess in the native of India or Africa than in the European, and we have good grounds for believing that it increases in prevalence during war in countries where amœbic dysentery is endemic. From all this it is clear that the relation between the dysentery and abscess is a contingent one—other factors determining whether the dysentery will give rise to abscess.

It is obviously more important, so far as the etiology of the disease is concerned, to ascertain the proportion of cases in which liver abscess is associated with dysentery than the frequency with which the latter is followed by abscess; and here the observations of the earlier physicians are available. The following table presents the percentage of cases of liver



cess found associated with dysentery or intestinal ulceration by some of the best observers in different countries:—

Observer.	Country.	Number of Cases of Abscess.	Percentage of Cases associated with Dysentery or Intestinal Ulceration.
Annesley . . . . .	India . . . . .	29	72·3
Waring, E. . . . .	„ . . . . .	204	72·2
Sanitary Commissioners . . . . .	„ . . . . .	509	53·0
Rogers . . . . .	Calcutta . . . . .	63	90·48
Sachs . . . . .	Egypt . . . . .	48	41·7
Kartulis . . . . .	„ . . . . .	500	55 to 60
Zancarol . . . . .	„ . . . . .	444	59·0
Kelsch and Kiener . . . . .	Algeria . . . . .	500	85·0
Smith . . . . .	Seaman's Hospital . . . . .	45	84·0

The statistics of the Sanitary Commissioner with the Government of India give the percentage of cases in which ulceration of the large intestine was associated with liver abscess for the period of six years—1896-1901. The statistics for 1901, which being the latest may be assumed to be the most accurate, give the number of cases of liver abscess in which a complete post-mortem examination was made at 59. Of these, the abscess was associated with ulceration of the intestine in 58·9 per cent; and in 41·1 per cent no ulceration was discovered. But three of the 23 cases, in which there was no intestinal ulceration, were associated with dysentery, which reduces the proportion of cases in which neither dysentery nor its lesions were present to 35·7 per cent. Rogers' figures shew the percentage of cases in which there was either clinical or post-mortem evidence of past or present dysentery. Both clinical and post-mortem proof of dysentery were present in 55·5 per cent only of his observations; post-mortem evidence alone in 20·63 per cent, and in 14·3 per cent there was clinical but no post-mortem evidence of previous dysentery. His observations, made in Calcutta, prove beyond doubt the almost exclusively enteric character of liver abscess in that city. In eleven of Sachs' cases in which dysentery was present no causal connexion between the intestinal and liver diseases was made out.

A few additional facts bearing on the relation of dysentery to liver abscess may here be noticed. Morehead failed to discover any intestinal lesion in twenty-one of his fatal cases of liver abscess. Kartulis, whose object was to establish the existence of an amœbic origin of liver abscess, was obliged to relegate eleven out of thirty-one cases, that is, 33·3 per cent, to the category of idiopathic abscesses, having failed to find any history of dysentery, any intestinal ulceration, or amœbæ in the pus or abscess-wall. In seven out of fifteen cases investigated by Kruse and Pasquale there was no history of dysentery, and no amœbæ present in the contents of the abscess. In four out of five cases of liver abscess occurring in Hong Kong, in 1903, there was no trace of dysentery, and no amœbæ were found in the pus or abscess-wall. Prof. Meyer, of Grant Medical College, Bombay, informs me that in a large number of cases of tropical abscess under

his case there was no history of dysentery, and often not the slightest trace of past or present dysenteric lesion.

A history of previous dysentery is not sufficient to stamp a liver abscess as amœbic, or even as dysenteric, if there are neither lesions in the bowel nor amœbæ in the pus of the abscess. Instances of large single liver abscess, following upon what was presumably a non-amœbic diarrhœa of the mildest possible kind, have been observed in persons who had never been out of England (1a). Neither is it safe to assume that a liver abscess associated with amœbic dysentery is necessarily caused by the amœbæ. Haasler, who was in medical charge of the German troops during the China expedition, in many cases did not detect amœbæ, but only cocci and bacteria of the colon group. When, on the other hand, amœbæ are present in the abscess, this may be taken as conclusive proof of its nature, even in the absence of dysenteric lesions, for an amœbic diarrhœa is frequently followed by abscess. There is some reason also for believing that amœbæ present in the bowel may give rise to liver abscess without causing diarrhœa or dysentery. A liver abscess, again, in a patient who has suffered some years previously from amœbic dysentery, may be the result of the dysentery, and yet not caused by an invasion of amœbæ. In other words, an amœbic dysentery may be the indirect cause of an idiopathic abscess.

What conclusions, then, are we to draw from the data before us? Examination of the figures as they stand shews that some of the best observers have failed to obtain evidence of a dysenteric or amœbic origin in from 15 to 30 per cent or more of their cases. That practically all the cases in Calcutta appear to be amœbic is no proof that the same holds true everywhere. It is impossible to ignore the observations of Kartz, Kruse and Pasquale, Koch, Councilman and Lafleur, Meyer and Chittre which have led them to admit the existence of an idiopathic abscess. I have seen a considerable number of cases in which a previous dysentery or diarrhœa could be positively excluded.

Late abscesses are those which occur after the patient has left the tropics for five, ten, or even twenty years, and has been free from all symptoms referable to bowel or liver. In most of these cases there is a remote history of dysentery, and in some, as in a case recorded by Jossierand, latent dysenteric lesions may be found in the large intestine. In most instances, however, no trace of dysentery is to be found post-mortem. These abscesses are generally sterile, and do not contain amœbæ. Some of them are probably due to a latent liver abscess, which, for some reason or other, has become the seat of an acute inflammatory process.

Mr. Cantlie has drawn attention to the somewhat frequent occurrence in the tropics of what he calls "suprahepatic" abscess. This he describes as "situated between the layers of the suspensory ligament of the liver, having as boundaries the peritoneum (limiting the space between the layers of the suspensory ligament) circumferentially, the liver below, and the diaphragm." The suprahepatic abscess is not a sequel of dysentery.

ushered in by hepatitis, but is caused, as Mr. Cantlie believes, . Although not a hepatic abscess in the strict sense of the existence and characters require to be remembered for reasons.

and up: the following forms of tropical abscess are met with:—  
 (a) Amœbic abscesses, forming the great majority of cases, associated with dysentery or diarrhoea, active or latent. (b) One or more abscesses are occasionally found in connexion with bacterial dysentery when it gives rise to deep, sloughing ulceration in the bowel. (c) Multiple pyæmic abscesses scattered through the substance of the liver, however, of more frequent occurrence than the single abscess, but by the fusion of these that the large abscesses are formed. (d) Idiopathic abscess, by which is meant one not caused by amœbic dysentery of the liver, is present in a very considerable number of cases, the prevalence varying apparently in different regions, and at different epochs. (e) The suprahepatic abscess, which has no connexion with dysentery, is to be looked upon as an extrahepatic form of abscess. (f) The late abscess, of tropical origin, remotely associated with amœbic dysentery, but in most cases idiopathic in its final result.

When a liver abscess is associated with dysentery what is the sequence in which they respectively appear? Annesley and Morehead considered many instances the hepatic disease precedes and gives rise to the abscess, and at the present day this view has the support of Kelsch. Of which I have notes, dysentery preceded the abscess in 21, abscess in 4, and in 9 instances the two diseases developed simultaneously.

In no fewer than 6 out of the 21 cases in which the dysentery preceded the abscess, it is noted that the hepatic symptoms appeared immediately on the cessation or followed closely on an exacerbation of the dysenteric flux. Major Rogers found either clinical or microscopic evidence of antecedent dysentery in all but two out of forty-seven abscesses.

**Connection to Malaria.**—When the malarial hypothesis of hepatic abscess was accepted it was taken for granted that the congestions of the liver during the fever were the determining cause of abscess formation; and now that this conception is exploded it is equally granted that malaria has little or no influence in the production of abscess. The precise action of the toxins of malaria on the liver has not been thoroughly investigated; hyaline degeneration of the hepatic cells has been observed by Flexner and others in connection with tropical tertian, which points to malaria as a predisposing cause of abscess. Not a few instances, however, are on record in which the nexus between malaria and liver abscess appears to have been more than the term *predisposing* implies. I shall only quote two of this kind:—Mr. Bell, of the Civil Hospital at Hong Kong, reported the case of a young officer of three months' service, in whom none of the ordinary causes of liver abscess were present. He was admitted

with enlargement of the liver, and his blood contained numerous parasites of malaria. The liver diminished in size under quinine, but the fever persisted, and, as a precautionary measure, the liver was explored and pus was found. A French officer was admitted with fever and liver abscess, but no dysentery or diarrhoea, and his blood shewed numerous parasites of tropical tertian. After the operation for liver abscess his temperature continued high ( $104^{\circ}$  F.). Under the action of quinine the fever disappeared. In cases of this kind it is impossible to exclude the influence of the malarial virus in the causation of the abscess.

**Personal Factors** — *Age*. — Liver abscess is a disease of adult age, but children are not altogether immune. Dr. Rolleston has collected references to 16 cases of "typical tropical abscess" in children, all of which were associated with dysentery. In two instances amebæ were found in the pus of the abscess. I may here add 2 cases in children aged respectively three and ten years, reported in the Hong Kong Hospital returns for 1903, in neither were amebæ or bacteria present in the pus or abscess wall. I find three deaths from liver abscess returned as occurring in an aggregate of 38,305 soldiers' children in India — a ratio of 0.08 per 1000. The age liability in percentages for the European army of India for the three years 1901-3 was as follows.

Under 20	20-25	25-30	30-35	35-40	40 and upward
4	10	22	20	18	26

If the average for a larger number of years were taken we should doubtless find a more uniform increase with advancing age, but the figures, as they stand, fully corroborate the inference of Blyden that liver abscess is "a disease of degeneration."

*Sex*. — Men are everywhere much more liable to liver abscess than women—the proportion being generally stated as 30 : 1. This I think is an exaggerated estimate of the difference in the liability of the sexes. The Indian statistics for 1901-3 give a death-rate of 1.5 per 1000 for the men and of 0.24 for the women — a ratio of, say, 7 : 1. The liability of women in the better classes would naturally be less than that of those attached to the army. The relative immunity of the female sex is the result of their more temperate habits, and of their being less exposed to the exciting causes of the disease. Van der Burg ascribes it to menstruation, and this may have a certain influence in diminishing liability to hepatic congestions and indirectly to abscess.

*Race*. — It is universally agreed that the natives of tropical climates are much less liable to liver abscess than strangers from cold latitudes, as is shewn by the figures for the European and native armies of India given above (p. 581). The experience of Haspel, who had charge of the foreign legion in Algeria, was to the effect that Italians and Spaniards were less subject to hepatitis than the natives of the north of Europe. The former, he says, "proved physiologically better adapted to the country."

*Habits*. — *Intemperance*. "The causes of liver abscess," says Aretz, "are intemperance, a protracted disease, especially dysentery, and

colliquative wasting." So far as alcohol is concerned, all modern observers agree with him in giving it a leading place in the etiology of the disease. Of 40 cases of liver abscess in which E. J. Waring noted the habits of the patients he found that 67.5 per cent were intemperate. "We seldom," says Cayley, "meet with hepatitis or liver abscess among total abstainers, except the pyemic form directly associated with dysentery." The comparative immunity of the natives of the East is largely to be ascribed to their temperate habits. Dr. Sandwith informed me that in Egypt the strict Mohammedan who follows the rules of the Prophet, although not exempt from liver disease, seldom suffers from hepatic abscess. "It is very rare among the peasant folk, women, and children of all races who are practically teetotalers." Conwell, in the same way, stated that "the native domestics who acquire European vices are equally or more subject to hepatitis than the European." The pernicious influence of alcohol on the liver manifests itself in temperate climates in giving rise to cirrhosis and other forms of hepatic disease. The mortality among publicans at home from diseases of the liver is six times greater than that of other classes of corresponding age. In India, alcohol does not, indeed, give rise to cirrhosis so often as in Europe, for the reason suggested by Maclean, that "the drunkard in India finds a shorter road to the grave." I would only add as the result of my own observations that the constant use of alcoholic liquors, short of intemperance, especially tipping between meals, powerfully disposes to liver abscess.

*Food.* An excess of animal food and the use of strong curries and rich pastries contribute, along with other causes, in disposing the European to liver abscess; but the influence of excesses of this kind has been exaggerated. The comparative immunity of the rich native, who often makes up for his abstinence from alcohol by gluttony, seems to shew that abscess of the liver is not the penalty specially attached to this vice.

*Acclimatisation.*—Prolonged residence in the tropics tends to increase rather than to diminish the liability of the European to liver disease and abscess. This will be seen from the following table, which gives the percentage mortality from liver abscess according to length of residence and the percentage of invaliding for hepatitis and liver abscess for the years 1901-3.

	Under 1 year.	1-2.	2-3.	3-4.	4-5.	5-10.	10 years and upwards.
Mortality from liver abscess .	18	7	10	12	14	25	14
Invaliding from hepatitis and liver abscess .	3	10	8	10	11	24	34

It will be observed that the mortality from liver abscess during the first year

of residence is very high, testifying to the newcomer's want of adaptation to tropical conditions. After the second year a steady rise in the mortality from abscess sets in, caused no doubt by the increasing inadequacy of the gradually deteriorating liver for the work thrown upon it. The amount of invaliding from hepatitis and liver abscess combined increases according to length of residence, and is a measure of the prolonged effects of climate and other conditions in determining functional and structural diseases of the viscus.

**Morbid Anatomy.**—*Number of Abscesses.*—From the discrepant results obtained by observers, it may be inferred that the proportion in which the abscess is single or multiple is a variable quantity. Of 288 cases analysed by E. J. Waring, the abscess was single in 61·5, double in 11·4, and multiple in 27 per cent. Niblock found the abscess single in 83, and multiple in 17 per cent of his cases in the Madras General Hospital. Prof. Meyer informs me that in Bombay abscesses are almost always single. The ratios in cases under my observation corresponded closely with those of Rouis, viz. 75 per cent single, 11 per cent double, and 14 per cent multiple. In one respect all these observations agree, viz. in shewing a large preponderance of single abscesses, a point of great importance, as it is these that almost exclusively recover on operation. Very different proportions are given by the Sanitary Commissioner for India; thus, in 509 autopsies during the six years 1896-1901, there were 34 per cent of single to 66 per cent of multiple abscesses. A very considerable number of cases of single abscess would, of course, be eliminated by operation, while the multiple cases would come to autopsy. This will account, to a certain extent, for the preponderance of multiple abscesses observed, but whether it explains the absolute reversal of the ratios hitherto observed may be open to doubt. Although a single abscess is frequently found in dysenteric cases, it is more commonly met with when there is no intestinal complication. The following table presents diagrammatically an analysis of the Indian results, shewing the relation of the single and multiple abscess to intestinal ulceration; it merits some attention on account of its bearings on the question of the existence of a dysenteric and non-dysenteric form of liver abscess.



18	<u>Multiple</u>	271	<u>Single</u>	73
	73 p.c.		27 p.c.	
	<u>Ulceration</u>	53		
		p.c.		
	509	cases		
	<u>No ulceration</u>	47		
		p.c.		
0	<u>Multiple</u>	238	<u>Single</u>	98
	59 p.c.		41 p.c.	

98	<u>No ulceration</u>	171	<u>Ulceration</u>	73
	57 p.c.		43 p.c.	
	<u>Single</u>	34		
		p.c.		
	509	cases		
	<u>Multiple</u>	66		
		p.c.		
140	<u>No ulceration</u>	338	<u>Ulceration</u>	198
	41 p.c.		59 p.c.	

Two or more large abscesses are not infrequently found close to one another, divided by septa, or communicating by a narrow sinus. These become united when one of them is drained—the septa giving way the equilibrium is disturbed.

*Site.*—The abscess is seated in the right lobe in from 70 to 80 per cent of the cases, in the left lobe in from 5 to 15 per cent, and in the Spigelii in from 2 to 5 per cent. Maclean found both lobes to be the seat of abscesses in 9 per cent of his cases. The upper and posterior part of the right lobe is the common seat of abscess. Much less frequently it occupies the concave surface. In either event it may be found superficially or deeply in the substance of the organ. In relation of the comparative frequency with which the right lobe is the seat of abscess, it will be borne in mind that it is six times the size of the left lobe, while Sérégé's experiments appear to indicate that the blood from the intestines is directed chiefly into the right lobe. Major Rogers states that the explanation, in respect to the superficial abscesses at the base of the liver, lies in the frequency with which amoebic dysentery invades the sigmoid colon and hepatic flexure, permitting the direct passage of the infection across the peritoneum to the right lobe.

*Form and Size.*—A hepatic abscess is rounded provided its uniformity of form is not interfered with; but it often becomes irregular, and even elongated, from the fusion of neighbouring collections of pus. The size of the abscess when it enters its surgical phase varies greatly, according to the age, stage of progress, and the resistance of the tissues. Some contain only two or three ounces of pus, from others one hundred or more may be evacuated. There is no difference in the idiopathic and dysenteric abscesses as regards their size.

*Effect of Liver outside the Zone of the Abscess.*—Rouis found that when the abscess was evacuated, the volume of the liver was normal in about 63 per cent of the cases.

per cent of his observations. In many cases its volume or weight is actually increased, but sometimes the greater part of the affected lobe is destroyed with a corresponding decrease in weight. According to Waring, the substance of the liver, apart from the abscess and the immediately surrounding tissue, is generally softened or otherwise altered in colour or consistence. Out of twenty-five observations recorded by Roux, the liver was found diseased in nineteen and apparently healthy in six cases. Kelsch and Kiener, on the other hand, conclude that the integrity of the parenchyma outside the abscess zone is the rule, not the exception. When the abscess has followed on long-continued dysentery, I have rarely found the liver throughout in a healthy state. The frequency with which perfect recovery follows evacuation of the pus proves, however, that the suppurative process must often be dependent on localised lesions, rendering a particular area liable to be surprised, as it were, by a microbial invasion, which it was, perhaps, only temporarily unable to resist.

*Formation and Contents of Abscess.*—Whatever differences exist in the modes of formation of the idiopathic and dysenteric abscesses respectively, these depend solely on the presence of amoebæ in the latter. The idiopathic variety is conceived as being more directly the result of an inflammatory process; the amoebic as more purely necrotic, the former associated with polymorphonuclear infiltration of the liver tissue, the latter characterised by the absence of leucocytic accumulations either in the necrotic tissues or in the capillaries. These distinctions are not absolute, since bacteria often co-operate with amoebæ in the production of the dysenteric abscess.

The smallest visible amoebic abscesses, according to Laffeur, have a diameter of from 1 to 5 mm., are spherical or ovoid, and do not empty themselves completely. On section a little glairy, translucent fluid exudes, leaving a yellowish grey spongy mass behind. The abscess extends by necrosis and breaking down of the liver cells around the cavity. Pale or yellowish necrotic foci are often observed around the central vein of the lobules, especially in the neighbourhood of the abscess, in which the hepatic cells are found to have undergone fatty degeneration, but which do not contain amoebæ.

The smallest idiopathic abscesses begin as one or more buff or yellowish spots which break down to form an abscess, from which the pus issues freely on section, being less viscid than in the dysenteric variety. When formed by the breaking down of one focus of suppuration, it is rounded in form, when several such foci, lying close together, unite, the resulting abscess is irregular in contour. In its earliest stage no lining membrane can be distinguished.

The walls of the larger abscesses—idiopathic and dysenteric—are irregular, and lined with a grey, ragged, shaggy, or shreddy membrane of granulation tissue undergoing necrosis superficially. Externally there is a zone of granulation-tissue mixed with degenerated liver-cells and connective-tissue elements, which merges in turn into a third zone in which

ective tissue is more abundant and more developed, and the liver better preserved but flattened by compression. In older abscesses the lining membrane is smooth, and a distinct fibrous capsule is formed which prevents the extension of the suppurative process.

The contents of the abscess in both varieties may be creamy, but are frequently of a chocolate colour, and viscid or watery—the so-called chocolate pus. Microscopically it consists of fatty liver-cells, debris of leucocytes in varying numbers, red corpuscles, and occasionally fragments of necrosed tissue. Charcot's crystals are often present in the pus. Bacteria are present in a varying proportion of cases, both of the idiopathic and dysenteric forms; and active amœbæ have been demonstrated in creamy pus as well as in chocolate-coloured pus.

Dr Rogers found cocci in sixteen out of thirty-four amœbic abscesses, and in six of these the possibility of accidental contamination could not be excluded. Kartulis found bacteria present in the pus or abscess-wall in eleven out of nineteen cases associated with amœbic dysentery, either included in amœbæ; and Kruse and Pasquale obtained positive results in five out of six cases. The possibility that bacteria are always present at the earliest stage of amœbic abscess cannot at present be decided. Kartulis cultivated bacteria from eight out of eleven, and Kruse and Pasquale from six out of nine cases of the idiopathic variety. The bacteria are most abundant in the capillaries between the pyogenic membrane and the liver substance, that is, in the zone undergoing necrosis. Morgenroth states that amœbæ were often absent from the pus of dysenteric patients in China, even in cases going on to abscess formation, and that the pus or lining membrane from such abscesses most frequently contained streptococci and staphylococci.

It will be observed that in a considerable number of instances liver abscesses are sterile. It is probable that bacteria are present in all cases of idiopathic abscess at the commencement, but die out at a later stage. This suggests that sterile abscesses may be caused, not by a pyogenic infection, but by some chemical substance derived from the bowel. Kruse and Scheuerlen have succeeded in producing aseptic suppuration experimentally by the injection of cadaverine and putrescine; but there is no evidence that abscess of the liver ordinarily arises in this manner by absorption of similar substances from the intestine. The bacteria found in liver abscess—dysenteric or idiopathic—are chiefly staphylococci, streptococci, the colon bacillus, and the *Bacillus pyocyaneus*.

Amœbæ are present in the pus or abscess-wall in the vast majority of cases associated with amœbic dysentery. In most of the instances in which they are absent, it may be reasonably assumed that they were present at an earlier stage. Amœbæ are most abundant in the smaller vessels. They are present in the pyogenic membrane, in the walls of the abscess, where they lie free in the tissues or within the capillaries, or in thrombi of the portal vein.

There may still be some doubt whether amœbæ by themselves, and without the co-operation of bacteria, are capable of initiating the suppurative

process. Musgrave and Clegg's experiments are not conclusive, as they were made with amœbe grown in symbiosis with bacteria. When infection takes place by the vena portæ, the amœbe generally carry with them or are followed by pyogenetic organisms, which demonstrably take an active part in the formation of the abscess. It is not so certain that the amœbe which reach the liver by the way of the peritoneum are in all instances accompanied by bacteria. Be this as it may, there can be no reasonable doubt that alone, or associated with bacteria, amœbe take an active part both in the initiation and extension of the dysenteric abscess. The mode in which they act is probably that suggested by Councilman and Laffeur, viz. —that the soluble products of the amœbe give rise in the first place to necrosis of the liver cells, and that the subsequent breaking down of the necrosed tissue is effected by their active penetrative and disintegrating movements. (For the description of Amœbe, see p. 18, and for their pathogenetic relation to Amoebic Dysentery, p. 530.)

**Pathogenesis of Liver Abscess.** The idiopathic and dysenteric abscesses are closely related etiologically and pathologically. Both are tropical, both affect the European more than the native, the European man more than the European woman, those addicted to alcohol more than abstainers; those subject to tropical malaria more than those who escape the infection; those exposed to fatigues and chills more than those not subjected to these influences. Both varieties occupy the same site, have the same symptoms, and present essentially the same lesions. The dysenteric abscess, if I may be permitted the expression, is an idiopathic one into which amœbe have found an entrance and impressed upon it certain peculiarities of secondary importance. In the idiopathic variety, the agents of suppuration are bacteria; in the dysenteric abscess, bacteria plus amœbe; but neither amœbe nor bacteria will as a rule give rise to abscess if the structure and functions of the liver be unimpaired. In all, or at least in the vast majority of cases, the necessary antecedent of abscess, whether idiopathic or dysenteric, is an inadequacy of the liver to cope with the work thrown upon it. How is this hepatic insufficiency caused, and why is it a special feature of tropical pathology?

That the constitution of the adult European is imperfectly adapted to the climatic conditions under which he has to live in the tropics is brought out in the complete alteration of the *culre* of disease which takes place in a number of adult Europeans transferred to India. The admissions for respiratory diseases falls from 57 to 32, while those of the digestive system increase from 101 to 142 per 1000. More particularly, hepatic affections, mostly congestive, give rise in India to 21 times, and dysentery to nearly ten times, the number of admissions that they do in England. This is largely the pathological outcome of physiological changes resulting in constitutions "set for cold" living and working under tropical conditions. In other words, a special susceptibility of the abdominal viscera to noxious influences—chill, alcohol, dietetic errors, fatigue, and such like—is a notable result of all that we include under the

term climate. A chill, which at home gives rise to bronchial catarrh, determines in the tropics congestion of the liver or intestines. Alcohol produces functional and structural disease of the liver more readily and constantly in warm than in temperate climates. The digestion, again, is weakened, and the use of a diet unsuited to the climate, and in excess of the requirements of the system, is a frequent cause of gastro-intestinal and hepatic disturbances which diminish the resistance of the liver to pathogenetic agents. But in many tropical countries the European encounters more specific causes of liver deterioration and suppuration, the most important of which are malaria and amœbæ; and these are all the more formidable on account of the functional disturbances and structural changes which the bowel and liver have undergone from climatic influences. Malaria is rarely, indeed, the direct cause of liver abscess, but the repeated congestions of the liver by which the fever is accompanied must be reckoned among the causes disposing to the disease. Much more important, however, is the part of amœbiæ in the causation of tropical abscess. The great frequency of liver abscess as a complication or sequel of amœbic dysentery is one of the most striking features in its etiology. This is explained first by the effects of the products of amœbic ulceration of the large intestine in giving rise to degeneration of the organ, and, as a consequence, to impairment of its functional activity; and secondly by the effects of these products, when in excess of the functional capacity of the liver, in exciting that form of hepatitis which so often precedes and precipitates suppuration.

1. As a cause of degeneration of the liver the toxins of amœbic dysentery rank in the first line along with climate and alcohol. In cases of amœbic dysentery Diamond found necrosis of the liver cells in the neighbourhood of the central vein, evidently the result of the dysenteric products absorbed from the bowel. If the subject of amœbic dysentery have been addicted to alcohol, all the more certainly will the amœbic toxins break down the resistance of the liver to microbial invasion. But even if the patient be of temperate habits, these toxins, by themselves, suffice to impair the integrity of the liver and to reduce its power of resistance. This explains why abscess of the liver occurs occasionally in abstainers as a result of amœbic dysentery, although rarely apart from this condition. The peculiar danger of this form of dysentery lies in its chronicity. The liver is subjected to the long continued action of toxic substances, capable of giving rise to degeneration even in a previously healthy liver.

2. Areas of degeneration thus established do not necessarily become the seat of bacterial or amœbic invasion, unless the degeneration is very far advanced. It is here that the effects of the products of amœbic ulceration of the bowel, in giving rise to hepatitis, come into play as a determining cause of abscess formation. The healthy liver is, within certain limits, not only capable of transforming such products and rendering them innocuous, but also of destroying the micro organisms which may happen to invade it (Roger). When, on the other hand, the functional activity of the liver has been seriously impaired, and its



physiological resisting power weakened, it is inadequate for the strain if at any time an excess of toxic substances be thrown upon it, or if the functional activity of the organ be temporarily suppressed or depressed by a chill, by a return to a cold climate, by a debauch, or other exciting cause. In these circumstances, a hepatitis is lighted up which may pass off, or recur and pass off again, but which, sooner or later, is apt to determine the invasion of the degenerated areas by amœbæ or pyogenetic bacteria.

About one-twelfth only of those suffering from amœbic dysentery develop abscess. Something more than the presence of amœbæ in the bowel is necessary to establish hepatic suppuration, otherwise the native would not be comparatively immune. The state of the liver itself, structurally and functionally, is an important factor in determining whether or not a dysentery shall end in liver abscess. I do not say that amœbæ or bacteria never give rise to abscess in a healthy liver. They seldom do so. The liver must previously be prepared for the reception of the pyogenetic organisms, and its resistance, in many cases, is finally broken down by the supervention of a hepatitis resulting from the incapacity of the liver, at a given moment, to deal with the products and organisms of dysentery.

It is remarkable how frequently an abscess arises on the sudden disappearance of dysentery, or after the disease is progressing to a cure, as shewn by the recurring headings of Kruse and Pasquale's cases, "Geheilte Dysenterie, Leberabscess." This sequence of events is too common to be accidental. Kelsch compares it to the metastasis of parotitis to the testes. The most probable, but not entirely satisfactory, explanation of this phenomenon is, that as the dysenteric ulcers are undergoing cure, the toxic matters, no longer discharged by the bowel, are absorbed, and, being too much for the functional capacity of the liver, give rise to hepatitis and abscess. The reason why bacterial dysentery is so seldom followed by abscess clearly is that, in most cases, it runs an acute course. There is no time for it to set up degenerative and inflammatory processes—the toxins formed being rapidly carried off by the stools.

The pathogenesis of the idiopathic abscess is essentially the same as that of the amœbic variety—impairment of nutrition and function, the establishment of foci of degeneration, work in excess of capacity, inflammation terminating in the invasion of the degenerated areas by pyogenetic bacteria. In short the pathogenesis of the tropical abscess may be expressed in the words *hepatic insufficiency*. The difference in the liability of the European and native soldier to abscess measures roughly the influence of climate, alcohol, food, and habits in its causation. These factors combined increase the liability of the European to abscess twenty-fold. The effect of alcohol by itself is measured by the difference of liability between the European who uses and he who abstains from alcohol, for which we have no reliable figures.

If this conception of the pathogenesis of liver abscess be accepted, there will be little difficulty in accounting for the etiological peculiarities



of the disease; its incidence on the European, on the male sex, on alcoholics, the influence of age and length of residence; its greater prevalence in countries where amoebic dysentery is common, and its frequent occurrence in patients who return to temperate climates during the winter season. I know of nothing in the etiology or pathology of the disease incompatible with this hypothesis.

**Symptomatology.**—*Acute Hepatitis.*—Abscess of the liver is frequently described as one of the terminations of acute hepatitis. The constitutional symptoms of hepatitis are fever, a coated tongue, constipation, scanty and high coloured urine, gastric disturbance, and, in some cases, slight jaundice. The local symptoms are pain, tenderness, or simply a feeling of weight, tension, or dragging in the hepatic region, usually increased on pressure. Pain in the right shoulder may or may not be present. An enlargement of the liver, sometimes very marked, generally uniform, but sometimes restricted to the right lobe, is the only other local sign of importance. Hepatitis, thus clinically portrayed, is not a fatal disease, as 86 per cent of the cases treated by Morehead ended in recovery. In 1903, hepatitis gave rise to only 3 deaths out of 354 admissions in the European Army of India. It may be safely affirmed that the vast majority of the cases returned as hepatitis are febrile congestions of the liver due to malaria, or to alcoholic or dietetic excesses, which have little tendency to end in suppuration, although indirectly they lay the foundation of future mischief.

But a form of hepatitis, etiologically more closely related to liver abscess, does occur. The patient suffers from an attack characterised by the symptoms above described, and often in a severe form. In a few days it passes off, recurs, and again subsides. After several such fugitive attacks, the same train of symptoms reappears, not to pass off as before, but is now premonitory of abscess. In most instances this non malarious hepatitis occurs in connexion with dysentery or diarrhoea—not necessarily amoebic—and then it should excite suspicion. This form of hepatitis may be regarded as due to the absorption of some toxin or other product of amoebae or bacteria from the bowel, and points to the inadequacy of the liver to deal with the poison. It always indicates a state of things that may at any time end in the invasion of the liver by amoebae or bacteria.

*Liver Abscess.*—A patient with liver abscess presents a sallow, muddy complexion, but is seldom distinctly jaundiced except when the abscess be so situated as to cause compression of the biliary ducts. When the disease is of some standing, he is emaciated and has a cachectic appearance. He suffers from anorexia and not infrequently from vomiting, especially if the abscess be on the under surface of the liver. There is often a history of dysentery or diarrhoea, if one or other of these be not actually present. Occasionally the patient is constipated. The urine in the early stages is scanty, and high coloured from urobilin; the urea normal in amount or somewhat in excess. When, at a later stage, suppuration has destroyed a considerable part of the parenchyma of the organ the

excretion of urea is notably diminished. Albumin in small amount is occasionally present. The more distinctive features, however, of abscess are fever, pain, and enlargement followed by a train of phenomena secondary to suppuration— hectic fever, profuse night sweats occurring during sleep, diarrhoea, and very occasionally delirium. It rarely happens that all the symptoms, primary and secondary, are absent, but in making autopsies one comes, now and again, quite unexpectedly upon an abscess which had not betrayed its presence during life. It is in cases in which the abscess runs a chronic course that the symptoms are obscure. The evolution of liver abscess is so irregular that it is impossible to delineate the disease in such a way as to shew the varying succession in which the phenomena develop. I shall content myself, therefore, with a review of the individual symptoms, indicating, at the same time, the way in which they are usually found to be associated.

*Fever.* In a large number of cases, fever, with or without rigors, is the initial symptom and is accompanied by pain in the region of the liver, and followed after a varying interval by enlargement. The fever may at first be continued or remittent, but when suppuration is established, it assumes an irregular quotidian type, with evening exacerbations, followed by profuse night-sweats. The fever may subside and recur during the progress of the disease. In a few cases hepatic abscess makes its appearance quite suddenly with severe rigors, high fever, and urgent vomiting, with nothing to direct attention to the liver, and may readily be mistaken for an attack of malarious bilious remittent fever. It is rare that liver abscess runs an afebrile course throughout, but instances of this kind apparently do occur. Pel records the case of a man who developed symptoms of liver abscess, for the first time, eleven years after his return from the East. The liver was enormously enlarged, and on operation gave issue to a great quantity of pus, but the patient's temperature continued subnormal throughout, and only rose to normal after evacuation of the pus.

*Pain* is practically always present at some stage in the progress of hepatic abscess, although very variable in degree and character. If its onset is sudden and severe, it will be accompanied by fever; otherwise it may persist for weeks without much rise in the temperature. More frequently a sense of weight, tension, aching, or dragging is complained of, rather than acute pain, but when suppuration takes place it may assume a distinctly throbbing character, or the pain may subside. When the serous capsule is involved the pain is of a stabbing kind, and, wherever situated, is frequently increased on deep inspiration, palpation, percussion, or succussion. When the abscess is situated in the right lobe, pain in the right shoulder and the region of the scapula is present, according to Sullivan, in one-sixth of the cases. Pain in the left shoulder is occasionally complained of when the left lobe is the seat of the abscess. These sympathetic pains are not, however, distinctive of abscess, as they are met with in hepatitis.

*Enlargement* is one of the most distinctive, though not one of the

earliest signs. When the disease has made some progress, enlargement will be recognised by inspection, palpation, or percussion. An enlargement of the right hypochondrium, a protrusion of the ribs, a widening of the intercostal spaces, a circumscribed bulging of the right costal wall, a swelling under the right costal arch or in the epigastrium may be visible on simple inspection. It is well to remember, however, that enormous collections of pus may be present in the liver without causing bulging. Oedema or redness of the skin is observed only when the abscess approaches the surface. Palpation not infrequently reveals downward enlargement of the organ. Unless the abscess is small and deeply seated, an extension of the area of hepatic dullness in some direction will be made out on percussion. As the abscess is generally situated in the upper part of the right lobe it is in this direction that an extension of the line of dullness is to be looked for, and this is, in fact, one of the commonest signs of enlargement. When the abscess has made some progress, the upper boundary of the dullness will be found to be convex.

*Tenderness.*—Localised tenderness of the liver on deep palpation is a very valuable sign not only of the existence but of the position of the abscess. The whole liver region should be carefully explored with the point of the finger pressed into the intercostal spaces when an abscess is suspected. *Fluctuation* is only to be made out when the abscess is near the surface. *Rigidity of the rectus abdominis muscle* is often present, but is not a sign of much diagnostic value.

*Decubitus.*—The patient is seldom able to lie on either side without pain. He generally finds most ease by lying on his back, with his shoulders raised, and his knees flexed, but the decubitus is variable.

*Symptoms connected with Lung and Pleura.* Patients suffering from liver abscess often seek advice for symptoms referable to the chest. They complain of a dry hacking cough dependent on irritation of the diaphragmatic pleura, or of oppression or dyspnoea from the bulging upwards of the diaphragm. The breathing is shallow, thoracic, and accelerated. Symptoms of basal pneumonia may be present before rupture of the abscess into the lung has taken place. The pneumonia in these cases is usually of a subacute type, with signs of consolidation, and crepitant râles on inspiration. When rupture occurs, the character of the sputum is quite distinctive. The pleura, also, is occasionally invaded by infection through the diaphragm before rupture. Friction, and the symptoms and signs of a serous or purulent effusion into the pleural sac, indicate this complication. Cerebral abscess is occasionally met with as a complication of liver abscess, but amebæ are not found in the pus of these abscesses.

*Symptoms connected with the Spontaneous Rupture of an Abscess.*—When the contents of an abscess burst into the peritoneal cavity, symptoms of acute peritonitis speedily ensue. Pain in the region of the heart, a sense of suffocation, and the physical signs of pericardial effusion indicate rupture into the pericardium. When the abscess bursts into the right

pleura, pain, dyspnoea, and the signs of pleuritic effusion or empyema are present. If it burst into the lung, the sudden expectoration of a brick red puriform matter will be observed, sometimes tinged with bile, preceded and accompanied by the physical signs of pneumonia of the base. The sputum after a few days assumes a chocolate colour and may contain amoebæ. Rupture of the abscess into the stomach is often preceded by gastric pain or irritation, and is declared by purulent vomiting, or the pus, more or less changed, may pass off by the bowels. In the case of rupture into the colon, pus will be detected in the stools, coinciding with a subsidence of the tumour. The opening of the abscess into the pelvis of the right kidney will be known by the discharge of pus by the urethra. Rupture into the vena portæ, the hepatic veins and the vena cava are seldom recognised during life. Cyr (7) gives the following as the situations of rupture in 159 cases:—Lung, 59; pleura, 31; pericardium, 1; peritoneum, 39; stomach, 8; intestines, 13; kidney, 2; inferior vena cava, 3; bile passages, 4; externally, 2. Perforation may take place in more than one situation in the same case.

**Duration**—The course of liver abscess is usually prolonged over several weeks or months; sometimes it is quite chronic; but instances are occasionally observed in which the disease proves fatal within a week or two. A case is recorded by Kelsch and Kiener of a patient who had been ailing for a few days only, and died six days after his admission into hospital. The mean duration of ten fatal cases complicated with dysentery, in which the time from the first appearance of hepatic symptoms could be fairly well ascertained, was nineteen weeks, and in sixteen cases of idiopathic abscess it was seven weeks. Abscess occasionally manifests itself for the first time in a person who has previously had dysentery from five to twenty years after his return to temperate climates. The pus in these cases is usually sterile, and their amoebic origin is doubtful. Jossierand records a case in which an abscess, occurring several years after the patient had left the tropics, was apparently caused by a latent dysenteric lesion in the intestine.

**Diagnosis.**—*Hydatid Cysts* are distinguished from liver abscess by their slow and painless growth, and moreover by not presenting the constitutional symptoms proper to liver abscess. A suppurating hydatid will generally be recognised by a history pointing to its commencement as a painless, slowly enlarging tumour. Should any doubt exist, an exploratory puncture must be resorted to, the discovery of hooklets in the pus being decisive. An *inflamed and distended gall-bladder* will be distinguished from an abscess of the liver by its pear-shaped form and mobility, and by the rule that it scarcely ever contracts adhesions to the abdominal wall or gives rise to inflammatory oedema of the overlying tissues. In many cases there will be a history of biliary colic, and the tumour will be found to have been soft from the commencement. *Pylephlebotic abscesses* are traceable to some focus of suppuration in the portal area. A uniform, tender enlargement of the liver, the acute course of the malady, the rapid development of grave constitutional symptoms, enlargement of

n, and the presence of jaundice are significant symptoms. *fever* may be definitely excluded if on examination of the blood ce of the malarial parasite and the presence of a polymorpho-ucocytosis are established. Although a leucocytosis is common other diseases its presence in an obscure affection of the liver is in abscess. Quartan or tertian periodicity of fever is characteristic a; the failure of quinine to arrest an irregular intermittent nts to abscess. Serious difficulty can scarcely arise in dis- g a *deep abscess of the abdominal wall* from one of the liver. A troduded into the cavity of the abscess will remain motionless spiration if the abscess be in the abdominal wall, but will follow atory movements if it be seated in the liver.

istory of the case with reference to tropical residence or a dysentery will always be very helpful. No lapse of time the possibility of abscess in the case of a person who has suffered from dysentery contracted in the tropics. In all cases exploratory puncture of the liver should be resorted to.

l-rays have proved of value in the diagnosis of some doubtful elsch and Nimier report two instances in which the diagnosis rmed by the discovery by radioscopy of the immobility and isplacement of the diaphragm, the obliteration of the costo-atic sinus, and certain appearances which were interpreted as ion of the lung around the point where rupture was about to

osis.—The prognosis of liver abscess must always be guarded. 22 admissions in the army of India for the three years 1901-3 than 286 of the patients died, and a considerable number were who doubtless increased the death-roll. The coexistence of sentery, a history of alcoholism, a cachectic, broken-down state stitution, and, above all, a plurality of abscesses, which cannot, be detected before operation, increase the gravity of the

The most favourable positions for spontaneous rupture of s are the lung and colon. Rupture into the pericardium is fatal, and the record of a solitary case of recovery after the f a liver abscess into the general peritoneal cavity serves only ise the fatal nature of this accident.

ylaxis.—Liver abscess should be looked upon as a preventable The death-rate in the European army of India, which in the a 1870-79 stood at 2.19 per 1000, fell to 1.24 for the period 0. This marked decrease is to be ascribed to improved sani- ore spacious and better ventilated barracks, and the spread of habits among the men. The idiopathic abscess, in particular, have become less frequent. As a very large proportion of the met with are consequent on amoebic dysentery the importance ating the amoebic infection is obvious. With this object, should be directed especially to the purity of the water-supply ie vegetables and fruits consumed in the raw state. The



other points enumerated under prophylaxis in the article on amœbic dysentery (*vide* p. 540) should not be overlooked.

Ardent spirits, in any form, should be shunned by those who wish to enjoy good health and length of days in the tropics. Excess in food, especially in animal food, is hurtful; and rich sauces, hot curries, and pastry should be avoided. In advising the European, however, as to his diet, the habits, tastes, and peculiarities of the individual should not be ignored. Some find themselves better on a diet chiefly animal, and have difficulty in digesting a vegetable diet in amount sufficient for their nourishment. In some cases the lighter wines, taken in moderation and along with food, are almost necessary as an aid to digestion. Needless exposure to heat and fatigue, and to chills after being heated, is to be avoided. Exercise, always short of exhaustion, should be taken regularly and at proper hours.

In attacks of hepatic congestion in connexion with malaria the prevention of reinfection as well as the treatment of the attack is to be aimed at.

Attention to the state of the bowels with reference to the functions of the liver is of more importance than is generally supposed. Constipation and looseness, if habitual, shew that something is sufficiently wrong to call for other treatment than the routine purgative or astringent. Hepatitis in connexion with dysentery, or simple diarrhœa of a recurrent or persistent kind, is a sign of danger even though the bowel symptoms are so mild as not to prevent the patient from following his usual employment. Our first object, in these cases, is the cure of the intestinal affection; but the hepatic symptoms should not be neglected. The patient is to be kept in bed, his diet restricted to milk or some mild substitute, and a few doses of ipecacuanha or salines, or both, are to be given. An occasional dose of blue pill or calomel is often followed by a relief of the hepatic symptoms and a general sense of well-being so marked as to be gratefully acknowledged by the patient. When symptoms of hepatitis supervene on the cessation of the dysenteric flux the free administration of salines is indicated.

In many instances in which hepatitis, with fever, enlargement and tenderness of the liver, and shoulder pains, has pointed to suppuration, the most marked relief has followed repeated punctures of the organ by an exploratory trocar in search of pus. The symptoms have promptly disappeared and the formation of an abscess has apparently been prevented. Mr. Cantlie says that his experience has taught him "that the abstraction of blood from an inflamed liver is the readiest way of relieving hepatitis." He recommends that 6 to 10 ounces be withdrawn in this way. There is very little risk in puncturing the liver if the large vessels be avoided. This method of depletion by an aspirator is deserving of trial, not only as a diagnostic procedure when pus is suspected but as a therapeutic measure in severe hepatitis, in order to avert threatened suppuration.

When the acute symptoms have passed or moderated, chloride of



ammonium should be given in fifteen to twenty grain doses, three or four times daily, and persisted in for a considerable time. The action of the bowels must be regulated by cascara, a combination of euonymin and rhubarb, or an alkaline saline, as the special features of the case may suggest. If pain in the region of the liver persist, repeated applications of liquor epispasticus over the seat of the pain will often give relief. But, above all, the habits of the patient as regards food, drink, and exercise should be regulated. If, notwithstanding these measures, the hepatic symptoms persist, a change to a temperate climate should be recommended. Such a change should never be made in winter, unless unavoidable, in which case the utmost precautions should be inculcated to prevent a chill. When abscess has formed, its treatment belongs to the domain of surgery. The earlier the existence of an abscess is ascertained, the greater will be the prospect of successful surgical treatment. This consideration is an additional reason for resorting to puncture in hepatic inflammation.

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A. D.

## PONOS

By ANDREW DAVIDSON, M.D., F.R.C.P.ED.

**Definition.**—Ponos (Πόνος, pain) is a disease of infancy and childhood, endemic in the Greek islands of Spezzia and Hydra, characterised by fever, enlargement of the spleen, cachexia, and hæmorrhages.

**Circumstances and Antecedents of Ponos.**—Sporadic cases of anæmia with enlargement of the spleen, known as *splenostomachon*, are met with in several parts of the mainland of Greece, and, like the splenic anæmias of infancy elsewhere, are generally associated with rickets, congenital syphilis, or malaria. The most striking peculiarities of that form of splenic anæmia distinguished as ponos are its restriction to and endemic prevalence in the two small islands of Spezzia and Hydra, its sudden and comparatively recent appearance, and its great fatality. There is nothing in the physical features or geological formation of these islands to explain its endemicity. Hydra is an elevated, rocky island situated a few miles off the coast of Argolis in the Peloponnesus, about 11 miles in length and from 2 to 4 in breadth, with a dry, barren, and calcareous soil. Spezzia, near to Hydra, is about  $6\frac{1}{2}$  square miles in extent, equally dry, but of volcanic origin. From the want of streams and underground water the inhabitants have to depend for drinking and all domestic purposes mainly on rain water stored in cisterns. This obviously increases the risk of the spread of infectious organisms. The population of Hydra, which before the year 1830 numbered 28,000, is now reduced to 7000, and that of Spezzia is somewhat less. The population of both islands has been decreasing of late years, and Diamantopoulos of Spezzia believes that this decrease, which has led to an improvement of the circumstances of those that remain, has had something to do with the diminishing prevalence of ponos. The inhabitants generally are poor and their houses insanitary. Their diet consists for the most part of cereals and vegetables. Malaria is entirely absent. Tuberculosis in its different forms is the prevailing disease, phthisis being particularly common among the women. Syphilis is somewhat frequent among the seafaring part of the population, but not apparently more so than among the same class in other countries. Rickets, according to Stephanos (\*), is rare in Greece, but among the few places in which it is more frequently seen he mentions the islands of Thera, Hydra, and Spezzia. This may be taken as evidence of the greater prevalence in these islands of conditions unfavourable to infant life—insanitary dwellings, defective nourishment, possibly an impure water supply—and these factors cannot be altogether foreign to the etiology of ponos. At the same time it must be remarked that as ponos is unknown in the island of Thera, where rickets is common, some other factor besides

se concerned in the evolution of rickets—something more specific—  
st be in operation in the islands of Spezzia and Hydra.

The first notice of ponos in medical literature was in the year 1855, when Roeser drew the attention of the Medical Society of Athens to the extreme frequency of enlargement of the spleen and anæmia in children in Hydra and Spezzia, and suggested that it might be due to the use of cistern-water. In the following year Fontana of Spezzia, while confirming Roeser's statement regarding its prevalence, pointed out the remarkable fact that ponos had only made its appearance in these islands within the previous three years. Practising as he did in Spezzia, recent appearance must have been within his personal knowledge, and no one has claimed for it an earlier origin. While it is quite conceivable, and not at all improbable, that cases of the same kind may have occurred sporadically for years before without attracting attention, the truth remains that a fatal disease, falling exclusively on infancy and childhood, emerged in a particular year into recognition, and rapidly attained quasi-epidemic prevalence.

Roeser's suggestion that ponos was due to the use of cistern-water was made in ignorance of its history. The water-supply was then what it had always been, and what it is in islands where ponos is unknown; but, on the assumption that the disease is caused by a micro-organism, a water-supply of this kind may not have been irrelevant to its spread and persistence. Another circumstance may have contributed to the almost epidemic diffusion of the disease at this particular time. The inhabitants of these islands, esteemed the richest in the archipelago before the Greek War of Independence, were suddenly reduced to poverty after 1830 by the transference of their trade to Syra. In the years immediately following this reverse in their prosperity there was much chronic misery, amounting to actual famine, which would tell adversely on the health of the infant part of the population, disposing it to any infection that might happen to be about. The coincidence in time and place is at least significant. It was while the distress was at its height, and in the localities to which it was limited, that a new disease of infancy made its appearance.

Since its first recognition ponos has undergone considerable fluctuations, sometimes declining so as to raise hopes of its extinction, then increasing in prevalence. The causes of these fluctuations have not been closely investigated, but are possibly related to the varying economic circumstances of the islanders. In the year 1881, when the disease was at an apex, the cases were estimated at 3·3 per 1000 of the inhabitants of Spezzia and 12 per 1000 in Hydra. These figures work out to a high proportion of the children under three years—the age-period to which ponos is practically confined. Assuming that the deaths from ponos fall on one-fifth of the total population, we have a mortality from this cause of 16·5 per 1000 in Spezzia and of 16 per 1000 in Hydra. The mortality from allied forms of infantile splenic anæmia in other countries does not usually exceed 1 per 1000 of the same age, and is probably much less.

If it be borne in mind that the figures given refer to a period when the disease had declined in frequency, we may conceive how fatal it must have been when it was at its maximum. We know nothing of any similar type of disease being other than strictly sporadic.

*Sources of Information.*—Occasional references to ponos are met with in the Greek press from 1835 to 1877, when the first systematic description of the disease, by Jeanakopoulos, appeared. This was followed by the accounts of Karamitsas and Stephanos (9) in the French medical journals, these forming the basis of all that has since appeared on the subject. Through the courtesy of Drs. Thomopoulos of Athens and Diamantopoulos of Spezzia I have been able to obtain a few additional data bearing on its etiology and clinical features, but unfortunately adding little to our scanty knowledge of the morbid anatomy or of the condition of the blood in ponos. The isolated position of the islands, remote from the centres of medical activity, the objections of the parents to have their children treated in hospital, and the insuperable obstacles in the way of *post-mortem* examination explain the backward state of our knowledge of the pathology of the disease.

**Etiological Features.**—Ponos makes its appearance after the eruption of the first incisors, and is most frequent from the eighth month to the end of the second year. Exceptionally, cases develop as late as the third or fourth year. Its age-period is thus different from that of the splenic anaemia associated with congenital syphilis, which falls chiefly on the first six months of life. Although hand-fed children are most liable to suffer, those brought up on the breast do not escape. The children of tuberculous parents are thought to be specially subject to ponos, and several members of such families are not unfrequently attacked in succession. This has given rise to the belief that the disease is tuberculous and hereditary. It is seldom found, however, that the patient is actually the subject of tuberculosis, but it has been remarked that some who have recovered from ponos have ultimately succumbed to phthisis, Pott's disease, or tuberculous arthritis. Children convalescing from acute febrile diseases, those nursed by cachectic mothers, those who have been suckled too long without the supplement of other nourishment, or have been brought up on improper food, furnish the greater number of victims to the disease; but ponos nevertheless occasionally attacks healthy infants of robust parents who have all along been properly nourished. Ponos may be associated with rickets; but, as a rule, no trace of rickets can be observed. Although no social class is exempt, the children of the poor are most liable to suffer. Boys are somewhat more subject to it than girls. Season has no appreciable influence on its prevalence. It is observed that the families of Spezziotas and Hydriotas who migrate to the mainland do not manifest the disease. Some 5000 natives of these islands, according to Xanthos, have established themselves at the Piræa but no case of ponos has been observed among them. On the other hand, it is stated by Jeanakopoulos that children of natives of the mainland born in Hydra or Spezzia may contract the disease.

**Anatomy.**—The viscera in one case of the disease were examined by Cornil, who found no evidence of leukæmia, tuberculosis,

The spleen was enlarged and firm, the capsule dense and the trabeculæ thickened. There was no notable pigmentary or any abnormal accumulation of leucocytes. The abdominal glands were generally normal, but a few were somewhat

There was commencing cirrhosis of the liver, the child had taken large quantities of brandy during its illness. The kidneys were atrophied. There were signs of chronic congestion and inflammation of the right lung, with necrosis of the first rib. The bronchial glands were normal or slightly enlarged. In an autopsy performed by Poulos the spleen presented similar appearances to those described by Cornil. The state of the other organs in this case is not

**cases of Ponos.**—Cases of anæmia with enlargement of the spleen are met with sporadically in infants and young children in all countries.

Possibly more than one disease is included under the name of splenic anæmia, but clinically they all present very much the same features.

Irregular evening fever, pallor of the skin, and a developing cachexia are symptoms common to all. Petechial spots, epistaxis, bleeding from the gums, or some other form of hæmorrhage is observed in more than half the cases. There is always a considerable enlargement of the spleen. In the majority of cases the spleen is moderately enlarged. The lymphatic glands, if involved at all, are to a trifling extent. Examination of the blood in these cases shows a decrease of the red corpuscles and hæmoglobin, more or less anisocytosis, the presence of nucleated red cells, and a few myelocytes.

In the majority of cases there is a leucocytosis with a relative increase in the number of white corpuscles which shew a well-marked polymorphism. The disease is often associated with congenital syphilis, still more frequently with rickets, and in a chronic course, and terminates fatally in more than half the number of cases.

There is evidently a great similarity as regards symptoms and course between this infantile splenic anæmia and ponos, the most notable difference being the much greater fatality of ponos. The disposing conditions are apparently identical. In both, the infant is born a life handicapped with a weak constitution inherited from the parents.

More frequently the disposition is induced later in life by unhygienic conditions, errors in nursing or feeding, or an acute illness such as bronchitis, diarrhœa, or other weakening ailment. In cases associated with morbid associations some differences become apparent. In cases associated with syphilis and rickets are not such frequent concomitants of infantile splenic anæmia.

It is not possible to institute a useful comparison between the morbid conditions of the two diseases, for in the case of ponos we have the records of many autopsies, while the splenic anæmia of infancy, according to the observations of Poulos, has no pathological anatomy peculiar to itself. At the same time the clinical course of the two diseases is very similar.

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same time it may be remarked that the state of the spleen in the two autopsies of which we have an account agrees, so far as the details admit of comparison, with that found in the majority of cases of infantile splenic anæmia.

When we come to the condition of the blood we find distinctions of more significance. Von Jaksch described, in 1889, under the name of anæmia infantum pseudoleukæmica a disease which he considered as distinct from leukæmia, on the one hand, and rickety anæmia with splenomegaly, on the other. This form was characterised by marked enlargement of the spleen, occasionally moderate enlargement of the liver, a high degree of oligocythæmia and oligochromæmia, along with a leucocytosis, "constant, persistent, and, in fatal cases, progressive," with little or no evidence of rickets. Imperfect as our knowledge of the condition of the blood in ponos is, we know that so far from leucocytosis being constant, it has not hitherto been observed in that disease. Leucocytosis is met with not only in the class of cases which come under von Jaksch's description, but in the great majority of cases, whatever may be their associations. Dr. Hutchison believes that in infantile splenic anæmia (and he apparently refers to all forms) "there is a general ratio between the extent to which the spleen is enlarged and the increase in the number of leucocytes." In ponos, on the other hand, great enlargement of the spleen is associated with leucopenia. Here we seem to have an important point of difference between the two diseases.

But a very decided leucopenia is found in a small percentage of cases of infantile splenic anæmia. It is uncertain whether this is merely a phase appearing at a certain stage of the disease, or whether a form exists in which the leucocytes are decreased throughout its course. If a class of cases of infantile splenic anæmia exist, characterised by leucopenia, it would, apart from its lesser malignity and sporadic character, be indistinguishable from ponos.

This leads us to notice the affinities of ponos with the splenic anæmia of adults. Anæmia and leucopenia are common to both. In both there is marked splenic enlargement not dependent on syphilis or other obvious constitutional disease. Unfortunately we do not know whether the Malpighian bodies undergo fibrosis and atrophy in ponos as in splenic anæmia, but this is rather probable than otherwise, seeing that fibrosis involving the trabeculæ often enough extends to the Malpighian bodies in the splenic anæmias of infancy. In ponos, as in splenic anæmia, the liver may remain unaffected throughout or undergo a terminal cirrhosis. Pigmentation of the skin may be present in both, and both are almost uniformly fatal. But there are also differences that cannot be overlooked. Splenic anæmia runs a much more protracted course than ponos, sometimes extending over nearly as many years as ponos does months. The age factor, however, has to be taken into account in estimating the importance to be attached to this difference. Gastro-intestinal hæmorrhage is very much rarer in ponos than in splenic anæmia. Ponos is a febrile disease, splenic anæmia is afebrile. With many points in common there are then no



ent grounds for regarding ponos as being an infantile form of splenic ia.

has been suggested that ponos may be related to some of the of cirrhosis of the liver occasionally met with in young children in and other parts of the tropics. The nature of these is imperfectly stood, but it has to be borne in mind that cirrhosis of the liver is a constant feature of ponos, and that when present it appears to always secondary to the splenic infection. The very few cases of otic enlargement of the liver and spleen, clearly independent of congenital syphilis and other known causes, which I have seen in the tropics, presented many of the features of Hanot's biliary cirrhosis. They their appearance in early childhood at a somewhat more advanced than that proper to ponos. The liver symptoms were not only the to attract notice, but throughout continued the most obtrusive res of the disease. Leucocytosis is not unfrequently observed in t's cirrhosis, and may be of some value in distinguishing it from similar maladies.

may appear extravagant to speak of the cachexial fever associated the Leishman-Donovan parasite in connexion with ponos. Cachexial has been observed in infants of the ponos age, but, unlike ponos, it is at any age. The possibility, however, that ponos may be caused by some protozoan infection cannot be altogether excluded.

**Nature of the Disease.**—In considering the affinities of ponos to affections accompanied by splenic enlargement and anæmia we taken no account of what is, after all, the most striking feature of the disease, namely, its endemico-epidemic character. In this respect is unique. We know nothing of an endemic type of splenic ia restricted to infancy and independent of malaria. Although the anatomy and the condition of the blood in ponos are imperfectly known, the endemic features of the malady are fairly well ascertained and it certain inferences regarding its nature.

We note in the first place the restricted area of its endemicity—not exceeding 26½ square miles. It is in the highest degree improbable that different kinds of splenic anæmia should prevail within such narrow limits. The bulk of the cases must be of the same nature and due to the same cause. The cause, again, is peculiar to the endemic area. The men of the islanders born on the mainland do not contract ponos, children born in the islands of parents who have migrated from the mainland are liable to be affected. These well-ascertained data are compatible with the view that ponos is merely an aggravated form of secondary anæmias associated with congenital syphilis, rickets, scurvy, defective hygiene, or errors of nutrition. It has been stated that infantile splenic anæmia may be caused by some poisonous product of perverted digestion consequent on gastro-intestinal catarrh. It is unnecessary to point out that this hypothesis would neither explain the prevalence of ponos within the endemic area, nor its restriction to that area unless we assume that the toxin is the product of a specific

fermentation set up in the contents of the bowel by a pathogenetic organism peculiar to Hydra and Spezzia. Dr Rolleston inclines to the belief that the analogous splenic anemia of adults is a chronic infective process having its headquarters in the spleen, and this hypothesis appears to be the one which best accords with all we know of *ponos*. Gastro-intestinal catarrh is seldom a prominent symptom at the commencement of *ponos*. The remarkable truth that *ponos* sprang into existence somewhat suddenly is also strongly suggestive of an infective nature. The history of epidemic disease furnishes not a few examples of germs at one time harmless exhibiting at another the highest degree of virulence. The germ of *ponos* possibly existed as a harmless organism in Hydra and Spezzia long before it assumed pathogenetic properties and became widely diffused.

**Symptoms and Course.**—*Ponos*, as a rule, commences gradually with slight fever, followed by loss of strength, pallor of the skin, and enlargement of the spleen. The child is found to be feverish at night. It soon becomes listless and sluggish in its movements. The skin is pale and sallow and after a time presents a distinct straw tinge, but jaundice is very rare. In some cases the fever is more pronounced from the outset, and of a quotidian, remittent, or irregular form. In the advanced stages of the disease the temperature often reaches 102°, 103°, or 104° F. The evening exacerbations are sometimes ushered in with slight chills, and pass off by sweats which are generally confined to the neck and chest. Towards the end the fever frequently assumes a distinctly hectic character. Within two or three weeks from the commencement of the general symptoms the spleen is found to be appreciably enlarged, extending one to two inches below the costal margin, and hard and firm to the touch. Occasionally a protuberance of the abdomen due to this cause is the first symptom to attract notice. It is possible, indeed, that the enlargement of the spleen may be present from the first appearance of the disease. The increase in the size of the spleen is rapid in proportion to the fever. After a time the organ is found to occupy the greater part of the abdomen, reaching to the iliac crest and crossing the middle line to the right. Spontaneous pain is seldom complained of, but tenderness and pain on pressure, although by no means constant, are sufficiently common to have bestowed upon it the name of *ponos*. The urine at the beginning of the illness is often extremely fetid; indeed, this condition is sometimes observed before any of the more characteristic symptoms are manifest, and is regarded as a precursor of the malady. This fetor does not, however, persist throughout the illness, but disappears in a few weeks or months. The urine is high coloured and often deposits a sediment of urates, but is seldom albuminous. In a certain number of cases a moderate enlargement of the liver becomes perceptible as the disease advances. In the time of its appearance, at least, it is secondary to the enlargement of the spleen. A trifling enlargement of the glands of the neck is observed in a few cases. The other accessible glands are normal.

The appetite is generally maintained to the end, but is notably

perverted, the patient greedily devouring the most unsuitable articles of food and often exhibiting a craving for wine or spirits administered by the parents, sometimes with the approval of the physician, in the belief that alcohol is beneficial in the treatment of the disease. Digestion is slow and difficult, frequently accompanied by meteorism, dyspnoea, and sweating, more rarely by vomiting. The bowels are always more or less disordered. At the outset, constipation is the rule, giving place at a later stage to diarrhoea, and at the close the motions often present a dysenteric character.

A cachectic state gradually appears and becomes more pronounced as the spleen enlarges. The child emaciates, the skin assumes a dusky colour, and œdema of the ankles, legs, and face sets in. Ascites is rarely present. Hæmorrhages are practically of constant occurrence, most commonly taking the form of petechial spots or ecchymotic patches on the trunk and extremities and bleeding from the gums. Next in frequency is epistaxis, which may appear during the course or towards the termination of the disease. Gastro-intestinal hæmorrhage is comparatively rare. The subperiosteal extravasations characteristic of infantile scurvy apparently have not been observed.

The *duration* of ponos is usually from eight to eighteen months, but it may prove fatal within six months, or be prolonged for two years. When the fever is high its course is rapid. Short periods of deceptive amelioration of the symptoms occur during the progress of the malady. Most cases terminate fatally. During the period of its maximum prevalence recovery was observed occasionally, and the earlier writers spoke not unhopefully of the issue when the disease came under treatment in the early stage and the circumstances of the parents were favourable. But as ponos has diminished in frequency it has increased in malignity. Diamantopoulos, speaking of ponos as it is met with in Spezzia at the present day, says it "invariably terminates fatally by itself or its complications." Equally emphatic is the testimony of Thomopoulos. "None of the patients," he says, "escape."

*Condition of the Blood.*—Few complete blood examinations, so far as can be ascertained, have been made in ponos. Karamitsas found a reduction of the red corpuscles and very marked leucopenia in two cases he examined. The leucocytes were so few that careful search had to be made to discern them. Other examinations of the blood have since been made with the result, according to Thomopoulos, of confirming the existence of leucopenia. In no instance, apparently, has leucocytosis been observed. But until the blood has been examined at the various stages of the disease, and the actual number of red and white corpuscles per c.cm. ascertained, the presence of leucopenia as a constant character of the blood in ponos cannot be accepted as scientifically demonstrated. Nothing has been ascertained as to the exact percentage of hæmoglobin, the presence or absence of nucleated red corpuscles, eosinophils, or myelocytes—points which must be known before we can determine the relation of ponos to other forms of infantile splenic anæmia.

**Treatment.**—Rational hygiene obviously occupies the first place in the treatment of ponos. When the mother is cachectic, a healthy wet-nurse should be got for the infant. This is said to have been followed in some instances by the best results. Premature weaning and protracted lactation dispose to the disease and should be avoided. When a suitable nurse cannot be obtained, the fresh milk of a healthy, well-fed cow, diluted according to the age of the child, should be given; and in the case of older infants, cream, beef-juice, or finely minced meat will be necessary. The dwelling must be clean, dry, and well ventilated, the clothing warm, and the child kept out of doors for the greater part of the day in the fresh air and sunlight. When the circumstances of the parents permit, removal from the locality is indicated. As regards drugs, quinine has appeared to be useful in controlling the fever, and in some instances is reported to have effected a reduction in the size of the spleen. Thomopoulos has not found its use prevent in any instance a fatal termination, even when administered from the onset of the disease, although in some cases it mitigates the symptoms. In the early stages experience is in favour of the use of iodide of iron and cod-liver oil. Bone-marrow suggests itself as worth a trial. When associated with rickets, in addition to the line of treatment just indicated, phosphorus might be cautiously tried in the case of older children; and when a syphilitic taint is suspected mercurials should be given. Orlandos of Spezzia states that the only instances of recovery which he observed were in children treated with wine or brandy. We give his experience for what it may be worth, but the mode of treatment is one for which theoretically at least, little can be said. One cannot get rid of the suspicion that alcohol may, to some extent, be responsible for the cirrhosis of the liver which sometimes sets in during the progress of the malady.

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A. D.

## BERIBERI

By Sir PATRICK MANSON, K.C.M.G., M.D., LL.D., F.R.S., and C. W. DANIELS, M.B.

SYNONYMS.<sup>1</sup> *Burbers, kakke.*

**Definition.** A specific form of multiple peripheral neuritis; characterised by special liability to implication of the phrenic and pneumogastric nerves, and a more or less marked liability to oedema of the connective tissue and serous effusion into the pleural, pericardial, or peritoneal cavities. The higher nerve-centres and the cranial nerves are very rarely implicated. The disease is apt to occur as an epidemic in institutions and amongst gangs of men. In certain tropical regions it is endemic. In cooler latitudes it may break out during the warm part of the year. High atmospheric temperature and abundant moisture favour its development, while defective food and bad hygienic surroundings are probably contributory influences.

**History.** The extreme antiquity of beriberi is undoubted. Strabo and Dion Cassius contain passages referring to it, or to a very similar disease which broke out in the Roman army when invading Arabia in 24 B.C. Chinese writers as early as the second century of our era make distinct allusion to it. According to Macgowan, it is referred to in the

<sup>1</sup> The local names for beriberi are infinite. In Java it is known by the natives as *Lesempon*, in Batak as *Pandjakot nibek*, or *nibek* (crystal sickness), in the New Guinea as *Pandjakot papua*, among the Malays as *Kaka imbat* (weak legs), in the French Antilles as *Maute de sucretes*, in China as *Huachuan* (cropsy), *de la region y thien*, in Brazil as *Pernecor* (ailing feet), in Matto Grosso as *Lachado*, in Ceylon it was at one time known as the *bad sickness of Ceylon*. In Japan it is sometimes called *Asike*; the term most commonly used there, however, is *Kakke*, a word which is now very frequently employed by European writers. It is well to remember that the term "kakke" is strictly synonymous with beriberi, and does not indicate a special Japanese form of the disease, as some seem to suppose.

There has been much useless and inconclusive discussion about the etymology of the word beriberi—the name officially recognised by the Royal College of Physicians of London. All that is with certainty known is that the word is of eastern origin. The attempts which have been made to settle its etymology amount to little more than ingenious speculation. Meyer Adress derives it from the Hindustani *ber*, a sheep, in allusion to the peculiar postural instances of the disease. Plateau derives it from the Siamese *berin*, *beribet*, *beribet*, stiff walking, tottering walking. Marshall from the Singhalese *Buripala*, weak movement. Berkens from the Hindustani, *Bharber*, swelling oedema, and Carter from the Arabic *bahr*, asthma, not *bahr*, a sailor, in allusion to the fact that it is a form of dyspnoea frequently met with among sailors in the Arabian seas. Simon says that during a visit paid to Ceylon he definitely ascertained that "beriberi" is a Singhalese word which simply means "a very bad sickness."

Certain medical writers, dissatisfied with the somewhat uncouth term beriberi, have suggested various Latin or Greek names, most of them referring either to the cerebral or to the paralytic phases of the disease, or indicating some hypothesis of its nature which may or may not be correct. Thus we have *Hydrops asthmaticus* (Rogers), *Synonymus beriberi* (Mason Good), *Myopathia tripartita* (van Overbeek de Meijer), *Neuritis multiplex* (Schwabe), *Paraplegia nephatica* (Swaving), *Seri pathosis perniciosa endemica* (Wernich), *Panneuritis endemica* (Balz).

Neiching, the oldest medical treatise extant and attributed to Hwang-ti (B.C. 2697). It is also mentioned in Japanese books of the ninth century A.D., but Scheube, who has devoted much attention to the literary as well as to the scientific aspects of beriberi, thinks that the allusions were borrowed from Chinese works; and he concludes, from the evidence of contemporary writings, that the disease appeared in Japan for the first time about the middle of the eighteenth century. Although in the earlier modern European works—from Bontius onward—relating to Eastern diseases, beriberi was distinctly recognised, and, so far as the knowledge of the times permitted, accurately described, latterly the subject seemed for a time to have somehow dropped out of medical literature—particularly the English—of tropical disease. Indeed, some authors were inclined to deny its existence as a specific disease, and to relegate it to some such category as anaemia, scurvy, malaria, or rheumatism. But the recrudescence of the disease in Brazil about 1863, the opening up of Japan to foreign intercourse, and the discovery that the “kakke” of that country was none other than the beriberi of the Indies, the epidemics in the Singapore gaol and in the prisons and mines of the Malay Peninsula, and in plantations in the Malay Archipelago, and the ravages of the disease among the Dutch troops in Atcheen, have in recent years concurred to force it again into notice.

Perhaps recent advances in neuro-pathology, the discovery that what were formerly regarded as ill-defined and unclassified groups of palsies depend on inflammation or degeneration of the peripheral nerves, and that these pathological conditions in their turn are attributable to certain poisons, have done more than anything else to forward the study and knowledge of beriberi; for it has been clearly proved by Scheube and Bälz in Japan, and, later, by Pekelharing and Winkler in the Netherland Indies, that beriberi is in fact a specific form of peripheral neuritis, an opinion now generally accepted. Until this generalisation was made, the symptoms and their singular grouping had received no satisfactory explanation. The recognition of this explanation of the clinical phenomena further involves the belief that the series of manifestations known as beriberi are essentially secondary, and that the primary source of the poison must be the antecedent real cause of the disease. The work of Hamilton Wright and others has done much to emphasise this point.

Efforts are being made to advance a step further in the search for the beriberi poison, which may be either a micro-organism or a chemical substance of microbic origin, but no conclusive results have as yet been obtained.

**Geographical Distribution.**—Although cases of beriberi have been reported as far north as the island of Saghalien, and although to our knowledge the disease has originated in the port of London among the crews of ships that had been in harbour for several months, its geographical limits may for practical purposes be stated as being about 45° N. (the island of Yezo) and about 35° S. (the city and neighbourhood



of Monte Video). Commencing at the eastern coast of Asia, beriberi occurs in Japan as far north as Hakodaté, being very common in the large towns of the empire, such as Tokio, Yokohama, and Kioto, especially in houses situated in the low damp districts. In Corea it is said to be prevalent, particularly on the south-east coast. We have met with no account of its occurrence in China to the north of the Yangtse River; but at Shanghai, and at all the treaty ports south of that city, in Formosa, and in Hong Kong, it is often met with. It has also been reported as endemic at Fatsan, a city a considerable distance up the Canton River; how much farther the disease extends into the interior of the Chinese Empire is not known, but apparently it is less prevalent in the agricultural districts than in the crowded towns near the coast. It was epidemic in Manila in 1882-83, and prevails there at the present time. It has also been reported from Tonkin and from Cochin China. In Singapore, Malacca, Penang, and in many parts of the Malay Peninsula it occurs with great frequency. It is even commoner in Java, Borneo, Sumatra, and in many of the islands of the Eastern Archipelago, the warm, damp atmosphere of which seems particularly suited for its development. Thus in Atcheen it has proved a scourge to the Dutch troops, native and European, and to their camp-followers. It is perhaps the most serious difficulty planters and miners in the Malay countries have to contend with; every year thousands of their coolies succumb to this disease, in some localities the mortality from this cause being over 50 per cent. Beriberi in Australia is usually a ship disease, as in the pearling fleets, or is met with occasionally as imported cases. Wetherall reported an epidemic among sixty aborigines who had been imprisoned at Kimberley, Western Australia, and Corlette and Molloy describe outbreaks among the Chinese in Sydney and Melbourne. The disease seems to have been common enough in India at one time; if it be rarer in recent years, this is possibly due to better barracks and improved hygiene in gaols, schools, and large public institutions generally. Recently we have accounts of outbreaks in Burma as high up the Irawaddy as Mandalay. According to Colonel Giles the disease popularly known in Assam as "beriberi" is really ankylostomiasis, but cases of true beriberi are still occasionally met with. Beriberi, formerly common in Ceylon, is now rare in that island. The disease known as epidemic dropsy, which visited Calcutta and its neighbourhood, and Mauritius in 1877-80, has also been described by some as beriberi; but although resembling this disease in certain respects, it appears to us to have shewn many differences—chief among which were the low mortality, the invariable presence of extensive dropsy, the short duration of the attack (three to six weeks), the absence of pronounced anæsthesia and paralysis, and the frequency of an eruption (*vide* article, p. 643). True beriberi does occur, however, in Mauritius and in the neighbouring island of Bourbon, where the chronic atrophic varieties were formerly called "barbiers." It is also met with in Madagascar, Zanzibar, Mombasa, and elsewhere on the east coast of Africa. It has often been seen on the west coast of that conti-

ment, and caused a terrible mortality among the coloured labourers of the Congo railway. In America beriberi has been reported from Cuba, Guadeloupe, Panama, Venezuela, and Cayenne. Of late years it has been extensively prevalent in Brazil and Uruguay, and has been encountered as far south as Monte Video. It is said to occur in the Sandwich Islands, and a definite epidemic occurred in Fiji amongst imported Japanese coolies, but when these left the disease disappeared with the exception of an occasional case amongst Chinese residents. Beriberi, if it occur at all, is certainly rare in Europe. It is conceivable, however, that some of the obscure cases of peripheral neuritis that crop up from time to time are of this nature. When, as in the outbreak at the Richmond Asylum, Dublin, in 1894, peripheral neuritis occurs in epidemic form and cannot be traced to arsenic, it is most probably beriberi.

As a general rule, in the countries mentioned beriberi is found principally in the low-lying districts along the coasts and on the banks of rivers; but mountainous districts and tablelands, provided they satisfy the necessary conditions of heat and moisture, are not exempt. Thus, according to Balz, beriberi occurs at Shinano in Japan at an elevation of 800 metres above the sea-level, and in the Malay Peninsula cases have been seen in ravines 3000 feet above sea level, but according to Wright the disease was really acquired at lower altitudes. In the endemic areas it always shows a marked preference for the low lying quarters of cities, for barracks, forts, hospitals, schools, gaols, mines, coolie lines on plantations, and for limited spaces wherein large numbers are crowded together. One of the peculiarities of its distribution is that in some districts, as on the island of Singapore, it is mainly a disease of the town, whilst in other districts in Malaya the large towns are relatively free.

In endeavouring to settle the geographical distribution of beriberi a must be borne in mind that our knowledge of the diseases of the natives of many of the countries within the limits indicated, though constantly increasing, is still defective. It is only at a few trading centres, for the most part on the coast lines, that there are satisfactory opportunities for gaining much information about the native diseases, and even at some of these places, from the absence of suitable hospitals, ignorance of native languages, and disinclination on the part of the people to consult European practitioners, investigation has been imperfect. Important diseases, even great epidemics, may exist among the natives of the interior, and even of the coast, and yet the resident Europeans may remain in complete ignorance of these events for a considerable period.

A remarkable feature about beriberi is its tendency to occur in ships. In the early days of European trade with the East, when ships were small and crews were large, when voyages were protracted, and when the fore-castle was crowded with ill fed, poorly clothed native sailors often accompanied by their families, beriberi frequently broke out among them; although, as was often noted, it rarely spread aft to the officers or European quartermasters. Even now beriberi is far from uncommon among the native crews of steamers trading to the East. The Seamen

Hospitals on the Thames are seldom without cases of the disease landed from such steamers. Not many years ago beriberi was so common in the Japanese Navy that one fourth part of the service was annually attacked. Similarly a large percentage of the natives and a few of the Europeans in the Dutch men of war in the East Indies suffer from the disease—more formerly than at the present day. Another curious point in its connexion with ships is that, like yellow fever, it sometimes seems to cling to particular ships, and to reappear in their crews year after year, though in such instances the intervals between the reappearances are often prolonged. Thus, in a Chinese gunboat, though scrupulously clean and well found, cases of beriberi cropped up annually over a number of years, appearing regularly among the crew soon after the onset of the hot weather. A remarkable and unexplained point in connexion with ship beriberi is that it is especially common in Swedish and Norwegian vessels—notwithstanding the generally fine physique of the crews and liberal diet.

**Etiology.**—Beriberi has been attributed to a multitude of different causes. Some of these, nephritis, for example, are so manifestly unconnected with the disease that it is unnecessary to discuss them. The following, however, may be enumerated. Malaria, scorbutus, intestinal parasites, occupation, bacteria, protozoa.

Taking a broad view of the occurrence of beriberi, the influence of malaria, scurvy, dysentery, and so forth as causal factors can be definitely excluded. As regards malaria, it would be easy to shew that whereas on the one hand beriberi is common in places, such as Singapore, where malaria is rare, on the other hand it does not occur in many of the countries most infested with malaria; that the parasites of malaria are only present in the blood of persons with beriberi when the two diseases co-exist, and that in the great majority of fatal cases there is no malarial pigment, old or recent, in the organs, and the leucocytic count is not that of malaria.

It would also be easy to shew that as regards *intestinal parasites* there is no relationship between the prevalence of such parasites as the ankylostome or the trichocephalus and the occurrence of beriberi. This is true both as regards the occurrence of the disease in different countries or amongst different races or classes in the same country.

*Occupation* may also be excluded. Thus, whilst beriberi in Japan and Bombay is commonest amongst sailors, in the Malay States it is commonest amongst miners, rare amongst those engaged in agriculture and in the urban population. Moreover, where two races are engaged in the same class of work, whether mining or agriculture, one race will be attacked, while the other may escape almost entirely.

*Improper Diet.*—This has often been advanced as the cause of beriberi, its claims will be discussed later on (p. 623), meanwhile, suffice it to say, they have not been established.

*Bacteria.*—The blood, other fluids, and the solid viscera have been frequently examined, and from time to time the presence of organisms

has been described. The best known of these organisms is the polymorphic bacterium described by Pekelharing and Winkler. All the more important recent observations, conducted with the necessary precautions, have shewn that the blood and solid viscera of persons recently dead in any stage of beriberi are sterile, and no organisms which will grow on culture media are to be found.

In the hollow viscera, especially the alimentary tract, organisms are of course numerous, and attempts have been made to isolate specific germs from these situations. Attention has been mainly directed to the throat, stomach, and duodenum, as being parts often shewing changes in beriberi. Organisms presenting peculiar characters have been found in or isolated from these situations, but in no instance has their pathogenetic character been proved.

*Protozoa* have been described by some observers, but all recent investigations conducted under favourable conditions have failed to shew that any such organism is present in blood, cerebrospinal fluid, serous effusions, or solid organs.

As will be presently explained, the group of symptoms indicated by the term beriberi is probably a late manifestation of an antecedent and probably extinct infection, with this in view it is highly desirable that the search for the specific organisms should be made at an earlier period and before the recognised clinical manifestations of the disease—the nervous symptoms—have set in.

Before discussing the various hypotheses as to the cause of beriberi which are seriously advocated by modern expert observers, there are a few outstanding points concerning the distribution and occurrence of the disease which ought to be considered irrespective of any hypothesis.

Beriberi occurs in all races and in both sexes, but children are rarely attacked. In any one country or place the incidence is mainly confined to one or only of several races resident there, and in ship epidemics it has been limited to one of several races that may be represented among the crews. In the Malay Peninsula the Chinese suffer most severely, but it is rare amongst the Tamils, and does not attack the Malays in the native villages. Europeans and Eurasians escape. Speaking generally, the disease is most common amongst the poorer classes of the affected race, and is most prevalent when work and money are scarce. This is well shewn in the Malay States, where the staple article of export is a commodity of fluctuating value—tin. The prevalence of the disease when the price of tin was low was much greater than at any time before or after this period when the value of tin was high. On board ship it is unusual for the officers to be attacked, the disease generally being limited to the occupants of the fore-castle, though in rare instances the officers suffer while the sailors escape.

*Period of Exposure*.—Persons who come into a district or institution, such as a prison, in which beriberi is rife do not manifest signs of the disease for some time. Among a number of fresh arrivals few cases

r in the first month; after this period cases begin to crop up, the greatest number being in the third and fourth months of residence. The beri incidence among new arrivals in the mining district of Sungei Ling, and the length of time between sentence and admission to hospital for beri in the Kuala Lumpur gaol, may be taken as examples. The following table for that gaol is abstracted from figures compiled by Travers :—

Cases of Beri-beri.	Month after Admission.							
	1st.	2nd.	3rd.	4th.	5th.	6th.	7th.	8th to 12th.
Sungei Ling Mines .	10	48	91	82	72	46	46	148
Kuala Lumpur Gaol .	11	45	67	40	27	25	25	8

Though these figures represent the common period of exposure, other observations shew that a much longer time may elapse. This period includes the time that passes before the poison—whether a germ or other nature—is introduced, the period of incubation, if there be one, the time that must elapse to allow the effect on the nerves to become manifest. The average incubation-period must, therefore, be considerably less than this period of liability to acquire the infection.

*Seasonal Variation.*—In most countries this is not absolute, but near the equator the admissions to hospitals and the deaths are apt to be numerous in the wet cool months. The more marked the climatic conditions the more marked is this difference. Cases are admitted and occur at all times of the year, and epidemics may occur in any season. The variation observed is more on a par with that noticed in the rate of occurrence of typhoid fever or of other zymotic diseases, than with that in diseases in which differences in the climatic conditions play a more important part. In subtropical countries beri-beri may be met only in the warm season.

The evidence is strongly in favour of the opinion that the disease is spread by or with man. In gaols the outbreaks, both at their commencement and throughout their course, are associated with the admission of new prisoners in the early stages of the disease. At the same time it could be noted that an epidemic soon dies out when such importation ceases; for, apparently, under the ordinary conditions of prison hygiene, outbreaks that develop in gaol do not seem to be capable of carrying on an epidemic for any considerable period.

Beri-beri introduced into countries previously unaffected may spread amongst the race that brought it. This was well exemplified in Japan, where a severe epidemic among the imported Japanese labourers lasted as long as they remained in the country, but did not attack other races, and disappeared when the Japanese left the islands. Other recorded importations, though at first confined to one race, the



disease extended to other races, so that more widespread outbreaks occurred. It may well be that originally the disease was introduced by the Chinese into the Malay Peninsula, where it is now widespread, and where it occurs amongst several races, though to a less extent than in the Chinese themselves.

The modern views as to the causation of beriberi may be divided into those which assume that the poison, or condition, causing the nerve lesions is manufactured or originates outside, and those which assume that it is produced inside the body of the patient. Under the first heading may be mentioned (1) nitrogen starvation; (2) arsenical poisoning; (3) chronic poisoning from some constituent formed in certain classes of food, such as fish or rice, and ingested with the food; (4) absorption by inhalation or otherwise of poison emanating from the ground or surroundings in places where beriberi occurs, *i.e.* place-infection; (5) personal infection. Under the second heading are those hypotheses to the effect that the poison is formed in the body as a result either of a primary microbial invasion producing a local lesion, or of some organism which forms this poison without causing such definite local lesion. The local lesions described are located in the alimentary canal, (1) gastro-duodenitis, (2) pharyngitis and other throat or mouth-lesions.

1. *Nitrogen Starvation*.—From a consideration of its geographical distribution, it appears that the disease is commonest in rice-eating races, especially among the classes in these races who, not being able to afford much food of other kinds, subsist mainly on rice. A diet deficient in nitrogenous elements is therefore a common feature in many of the outbreaks of beriberi. Observations in Japan were in favour of the view that such a diet was the real *cause* of beriberi. Up to 1883 the cases in the navy of that country averaged over a quarter of the strength, and in that year there were 1236 cases of beriberi in a force of 5349 men. In 1884 the dietary was changed, a larger proportion of nitrogenous food being given, and in 1885 there were only 41 cases, in 1886 only 3, and since then practically none. Takaki, who was the first to propound the nitrogen-starvation hypothesis and who brought about these dietetic changes, naturally regards these figures as a proof that his view as to the influence of diet on the causation of beriberi is correct. It must be recognised, however, that other extensive changes were made at the same time, and that the general hygienic conditions were vastly improved. The publication of Takaki's views and statistics led to a careful consideration of the diets in gaols where epidemics were frequent, such as those in Singapore and the Federated Malay States, but in spite of diets as physiologically correct as that adopted in the Japanese navy, outbreaks of beriberi still continue, and bear little or no relation to the changes in the diets. "Nitrogen starvation," moreover, is common in all countries amongst the poorer classes, and yet beriberi is limited in its distribution.

(2) *Arsenical poisoning* was suggested by Prof. R. Ross on account of the close resemblance between the neuritis of beriberi and that occurring



in the drinkers of beer contaminated with arsenic, and because analyses of hair of beriberi patients have in some instances shewn an excess of arsenic. It has been shewn, however, that in the Singapore gaol all the articles of diet were free from arsenic though beriberi was prevalent in the institution at the time of the analysis. The occurrence of beriberi in the tin mines of the Malay States bears no relation to the amount of arsenic in the mineral; and in a mine in which arsenic is abundant, the Tamils, though equally exposed to risks of arsenical poisoning, almost invariably escape whilst their fellow-labourers the Chinese are attacked. It is rare for arsenical neuritis to occur without any previous symptoms of arsenical poisoning, yet in beriberi, symptoms such as are unquestionably due to arsenic are extremely rare. The skin lesions of arsenical poisoning, for example, are not met with in beriberi.

(3) *Infected or decayed food* is by many considered to be the cause. The two articles of diet incriminated are fish and rice. *Fish*, whether fresh or salt, can be excluded, because during some of the prison epidemics, such as that in Kwala Lumpur in 1900, no fish at all was eaten.

*Rice* forms a large proportion of the simple diets adopted in all tropical gaols, and in many it is the only cereal consumed. In these prisons outbreaks of beriberi have occurred from time to time, quite irrespective of the proportion of rice in the dietary. Without any change in the relative amount of the rice or other food constituents an epidemic may originate, decline, and die out. If, therefore, rice be the cause of beriberi, it is not a question merely of the quantity of rice consumed, but of the amount of the "poison" it may contain, which must vary greatly. This "poison" cannot be of the nature of a living germ, for in some of these institutions the rice is boiled under pressure and has been shewn to be sterile after cooking; moreover, it may appear sound and free from visible signs of disease or decay. A rice-conveyed living germ or an organic poison produced by gross putrefaction are therefore excluded.

A more important hypothesis is to the effect that rices prepared in certain ways may develop a poison which is not decomposed by boiling, and that this poison taken continuously in small quantities causes the neuritis. Market rice before it is husked is either simply dried; or it is dried, then boiled or steamed, and again dried before husking. The forms of rice suspected by the advocates of the rice-poison hypothesis, notably Braddon, are those in which the rice is prepared from the padi by husking without previous boiling or steaming. Braddon believes that the husk contains a fungus which is able, after the grain is husked, to penetrate into the bruised and decorticated grains. It is further supposed that only certain crops, or the rice from certain places, contain this fungus, and that therefore it is only a small proportion of the eaters of this class of rice who will be attacked. In support of this hypothesis certain well-ascertained facts are cited, such as the comparative immunity of the Tamils, who steam or boil the rice before husking, as compared with the Chinese, who use rice husked without previous boiling.

Further, in a fair number of instances an outbreak has ceased suddenly when the rice has been changed. But sudden cessation of epidemics is so common in the histories of outbreaks of beriberi, even without any change in the diet, that little stress can be attached to this. In most of such instances, in addition to the change of rice other changes affecting the hygienic condition, and particularly affecting the possibilities of infection, had been made, so that besides the change of rice many additional factors were introduced that materially detract from the significance of the observations. In several instances, such as those recorded by Drs. Travers, Wright, and Durham, two groups of men were for months fed on portions of a mass of rice cooked in the same place, and yet though numerous cases occurred in one group there were none in the other. In view of the importance of the question further experiments are urgently needed on a large scale, and under conditions sufficient to exclude the possibility of infection, mediate or intermediate. Careful criticism shews that the available evidence in favour of rice as an essential cause or as containing the real cause of the disease is weak; and there are so many facts in favour of the opinions that either infection from man to man, or that which has been designated "place-infection," is the method by which the disease is spread, that in the absence of conclusive evidence that rice is a factor we are justified for the present in disallowing that hypothesis.

(4) *Ground-, earth-, or place-infection* has many advocates. Instances in which successive occupants of houses, or even beds, have been attacked can be adduced. In some institutions beriberi is always present, though varying greatly in prevalence from time to time. In other institutions and in ships its occurrence year after year has been noted; in other instances the intervals between the successive reappearances of the disease are more variable and often prolonged. According to this hypothesis the earth or buildings contain a germ which in certain circumstances, such as warmth and dampness, multiplies; its toxic products diffusing are absorbed in air, food, or otherwise, and so cause the neuritis. As in the case of other hypotheses constructed to suit certain points in the etiology, some of the facts are not completely explained by this hypothesis. Thus, in those instances in which the intervals between outbreaks are prolonged, months or even years intervening, the infection is either not permanent, or if permanent is only active at uncertain, irregular times, which, so far as is known, are not obviously related to any meteorological or other condition. Again, in some places for example certain gaols, the occupants of the ground-floor do not suffer more than those on the first or second floors, an occurrence that is difficult to explain on the supposition of an infected soil. A common argument in favour of this hypothesis is that recovery is more certain and rapid in persons removed from an infected locality, and undoubtedly a markedly beneficial effect often follows such a change; but it is not essential for recovery, and in many instances in which some patients have been removed and others have not, recovery has been more rapid and the

case-mortality lower among those remaining in the infected locality than amongst those removed. The low rate of mortality, 3-5 per cent, in many institutions in which the patients are not removed from the endemic area tends to shew that continued absorption of a poison does not occur.

All who believe that some kind of infection is at work in beriberi will admit that in some cases the infective agent remains in the rooms and articles of personal use for some days or even longer after the removal of the patient, though the infective agent cannot maintain its extra-corporeal existence for an indefinitely prolonged period in earth, rooms, or clothing. There is nothing in the hypothesis of place-infection incompatible with the observation that in some instances the disease is carried from one place to another, and that in others, as in the case of the Japanese coolies in Fiji, though introduced in this manner, its spread is extremely limited, for all soils and conditions may not be suited for the development of the organism producing the poison. According to this hypothesis the organism may possibly be normally present in some soils, though it is certainly not so in most, even in Asia. This hypothesis, like so many others, does not explain the immunity of certain races and classes, such as that of the Tamil mining coolies in the Malay States. Tamils and Chinese work in the same or in closely adjacent mines, and live in similar barracks close to these mines. Beriberi rarely occurs amongst these Tamils, but the Chinese suffer severely from it. On the other hand, when Chinese and Tamils are under precisely the same conditions, as in the larger prisons, individuals of both races acquire the disease; the immunity, therefore, is not racial.

(5) *Personal Infection*.—The hypotheses based on the belief that the disease spreads from man to man are constructed on analogies with other known diseases, and particularly with diphtheria. Though the nerves affected differ to some extent in diphtheria and in beriberi, the nerve-changes are, according to Hamilton Wright, practically identical in the two diseases. As might be anticipated, careful search has been made for some primary lesion, even if only of a trivial character, to correspond with the throat condition which precedes diphtheritic paralysis. The gastro-duodenal condition, considered by Hamilton Wright as the primary lesion, will be discussed later. The pharyngitis suggested by Dr. Durham as a possible representative is too inconstant; and the same may be said of various oral and dental conditions met with in some cases of beriberi and in some outbreaks in the majority of the persons affected. No constant lesion has been proved to precede the neuritis, and there is no antecedent lesion or definite condition which enables us to predict the onset of the paralytic disease we know as beriberi.

The present state of our knowledge only admits of the following conclusions: that the real causal agent is capable of transmission by man from place to place; that when introduced into a healthy community, such as the inhabitants of a gaol, the disease spreads to a limited extent only, unless fresh cases be introduced; that though close attention to

hygienic conditions, especially to diet, may further restrict, it does not prevent this spread; that the disease is not conveyed by air or for any distance by water, and that there is no satisfactory evidence that it is spread by food-contamination of food or water; that the disappointing results of disinfecting dwelling places, such as coolie lines or prison cells, is opposed to the opinion that the disease is spread by inhalation; that no gross lesion is a constant precursor of beriberi, and, therefore, that if the cause of the disease be a micro-organism, vegetable or animal, it must be one that produces the neurotoxin without giving rise to any marked and constant local lesion, or affecting the general health; that it would then resemble some other diseases due to nerve-poisons in which the primary lesion may be insignificant or imperceptible, as in some cases of tetanus. If it be assumed that beriberi is a germ disease, and that this germ is introduced into the body, it may be that it produces the characteristic lesions by means of a poison elaborated in the blood or in the contents of the alimentary canal.

*Infection and how conveyed.*—Assuming that beriberi is a germ disease, it is important to determine, if possible, the mode in which the infection is conveyed.

In many instances one member only of a family is attacked, and even a person in close contact with those attacked may entirely escape. Beriberi is very rare amongst medical men, hospital attendants, and prison warders, even when the inmates of such institutions suffer severely. Therefore, if beriberi be directly communicable from man to man it can only be so to a very slight extent; moreover, this mode of transmission does not explain the frequent epidemics or the irregularity of its spread in an isolated community.

Our knowledge of the way in which disease is conveyed by intermediate hosts, mainly insects, raises the question whether this form of infection plays any part in the case of beriberi. The occurrence of outbreaks on board ships at sea limits the possibility of such a form of infection to a very few insects. As possible carriers or intermediate hosts, mosquitoes can be definitely excluded. In some of the gaois mosquitoes are not numerous and belong to well-known domestic species. *Culex fatigans* is the commonest, but *Stegomyia scutellaris* or *fasciata* and *Mosquito* *rossi* are also found. Beriberi is unknown in many places where the mosquitoes occur. A hypothesis based on the idea of mosquito infection does not explain the freedom of night-warders and of other gaol officials, nor the rarity of the disease among the Tamils in the Malay States who sometimes occupy with impunity coolie-lines near those crowded with severely infected Chinese. Most of the biting flies, including "sand flies," can also be excluded, as they do not occur in some of the prisons in which the disease prevails. The same is true as regards ticks. Of other blood-sucking insects, the only ones that need be considered are fleas, bed bugs, and lice. Fleas can be excluded as they are extremely rare in prison-cells and ships. Bed bugs (*Cimex lectularius*) are not uncommon

are difficult to extirpate, and as far as beriberi incidence in prisons concerned they might possibly be the carriers; but, in the Malay States, outside the prisons, Tamils and Sikhs are at least as much infested by these pests as the Chinese who suffer from beriberi. The weekly bi-weekly oil bath taken by the Tamils is no protection from these pests.

There are certain facts which encourage the study of lice as possible transmitters of beriberi; these insects are found in all races, though lice other than *Pediculus capitis* are very rare in the Malay States. Pediculi are restricted to certain regions of the body; *Pediculi capitis*, for example, are rarely found on hairy parts other than the head. The variations in colour and markings of pediculi infesting the different races of mankind appear to be not only an adaptation to surroundings, but may imply a preference for one of the same race in the event of change of hosts. The customs of the different classes of a community as regards treatment of the hair, use of oils, frequency of washing, and so forth, may vary greatly, whilst in the prisons all are treated alike. Pediculi only occasionally and accidentally change their hosts, but this occurs sufficiently often to make it possible that these insects might be the means of conveying disease to other individuals. The persons thus infected would probably be of the same race and class as the individuals from whom the lice were derived, because the treatment and character of the hair is similar. The more crowded and poorer classes would necessarily be most liable to be infected in this manner. Pediculi, therefore, appear to be the only possible transmitting living agents of beriberi. There is no proof, however, that it is so conveyed. The most that can be said in favour of such a hypothesis is that it is compatible with many of the peculiarities in the race, class, and sex-incidence of the disease.

The possibility, therefore, that the virus of this disease is conveyed by pediculi or other ectozoa is worthy of serious investigation, and makes it important that every effort should be made to exterminate all such pests in those institutions and communities in which beriberi occurs.

**Pathological Anatomy.**—The morbid changes in fatal cases of beriberi are chiefly in the nerves. In addition, the hydropic form shews a general serous infiltration of all the connective tissues, and increase—sometimes to a very considerable extent—in the serous exudation in the pericardial, pleural, and peritoneal sacs. Small ecchymoses under the serous membranes are not uncommon, and are probably produced during the death agony. Occasionally intramuscular hæmorrhages and smaller extravasations within the sheaths of the nerves are met with. The lungs are often œdematous and flaccid, even shortly after death. All the cavities of the heart are dilated, but the right more so than the left. A slight degree of hypertrophy appears to be the rule, as the weight of the heart is on the average above normal. The myocardium is fatty and friable. There are no characteristic lesions of the abdominal viscera.

The special lesions are in the peripheral nerves and in the muscles supplied by them; they closely resemble those in post-diphtheritic paralysis.



The later and coarser lesions were carefully studied by Bälz, Scheube, Pekelharing and Winkler, and others.

Hamilton Wright describes the histological appearances in the early and rapidly fatal cases as consisting only of slight alterations in the *trophic cells* of the affected neurons. In these neurons, in preparations stained by Marchi's method, there is only a slight black flecking about the nodes and scattered discretely along the internodes; no coarse changes are apparent, although in these acute cases almost every fibre of the *vagus* may be affected. The parent cells as shewn by Nissl's method are swollen, the nuclei eccentric, and the Nissl's bodies in the processes and in the periphery of the cells absent or altered. The changes at this stage are so slight that Wright believes complete recovery would be possible if the causal poison were removed or counteracted.

In a rather more advanced stage he describes the nuclei as being swollen and dislocated, and the processes denuded of Nissl's bodies and almost wholly of the fine deposit derived from them. The central Nissl's bodies are diminished in size. In the dependent fibres the altered myelin is often broken up into fine globules, but the irregular nodal and internodal flecking predominates. The important feature at this stage is not the degree but the extent of neuronal change. In fact, the changes in the vagal cardiac and accelerator fibres are so widespread that the freeing of the heart from its nervous control results in death before sufficient time has elapsed for more advanced nerve-changes to occur.

In the more advanced stages a proportion only of the neurons are implicated, and many seem to have recovered completely. In the others the cells show extensive changes, the nuclei being dislocated, and the Nissl's bodies having disappeared. The terminations of the nerve-fibres are in an early stage of atrophy—Wallerian in appearance. The myelin is altered and broken up into globules more or less coarse, as described by Scheube, Pekelharing and Winkler, and others. When the morbid processes have advanced to this stage, recovery of the function of the affected neurons is impossible.

The changes described have been found not only in the nerves of the limbs, but also in the pneumogastric and phrenic nerves; in the laryngeal branches of the former, and in the nerves of the heart.

According to Pekelharing and Winkler, the *sympathetic fibres*—so numerous in the pneumogastric—present evidence of implication in their finely granular appearance and in the proliferation of their nuclei. Similar appearances have been noted by Scheube in the renal sympathetic.

The affected *muscles* are usually sodden and pale; occasionally in the atrophic forms of beriberi they are dry and shining. In both forms the individual muscular fibres shew granular or vitreous degeneration, striation being faint or absent, and the fibres much wasted or reduced to sarcolemma only. There is also an increase of nuclei, together with overgrowth of interfascicular connective tissue, particularly along the course of vessels. Young muscular fibres, or what from their clear striation are presumed to be such, are often visible among the degenerate



l fibres. Evidence of myocardial degeneration, extremely variable in amount, is constantly present, and here and there among the muscular fibres foci of inflammatory infiltration may be detected with the microscope.

Changes in the *alimentary canal* have been described as possible indications of the primary condition to which the nerve-lesions are secondary. From time to time many observers have noted in some cases of beriberi congested condition of the stomach and other parts of the alimentary canal. This condition was carefully studied by Hamilton Wright, who describes the lesion as a gastro-duodenitis, the mucosa shewing moderate congestion, intense inflammation, or hæmorrhagic infiltration. According to his observer, in all cases the pyloric end of the stomach and the *ulæ conniventes* of the duodenum are the seat of discrete or more or less confluent hæmorrhagic extravasations, or the crests of the *valvulæ conniventes* are deeply injected. When these changes are extensive a thin layer of blood-stained mucus can be stripped from the underlying mucosa. Sometimes the changes are met with over a more extensive area, even as low down as the cæcum. In these affected areas the same observer also describes a large bacillus with rectangular ends. It retains its stain when treated by Gram's method. This organism has not been isolated and has not been found constantly by other observers in the lesions or in the contents of the alimentary canal. Dr. Hunter considers these organisms to be a secondary invasion.

Wright maintains that gastro-duodenitis is present in all early cases, that it disappears in a comparatively short time (often two weeks or less) after the onset of the nerve-symptoms, and that, judging from clinical evidence—gastric symptoms and epigastric tenderness—these changes precede these changes. He concludes that this gastro-duodenitis is the primary and essential lesion in beriberi.

No doubt gastro-duodenitis often occurs in beriberi, but it is certainly invariably present in the early stages, as Wright asserts. The evidence that the morbid changes in the stomach and duodenum are a necessary precursor of beriberic paralysis is not conclusive; it is quite possible that this condition is secondary to the implication of the pneumogastric and to the passive congestion resulting from the cardiac dilatation and consequent upward blood-pressure.

**Symptoms.**—The onset is variable. In some instances the paralytic symptoms appear suddenly with at most an ill-defined prodromal stage, lasting one or two days, during which the patient is able to perform his ordinary work. More commonly, before an attack of beriberi is fully declared, there is a premonitory stage of longer or shorter duration. For several days, or perhaps weeks, the patient feels languid, is fatigued and short of breath on slight exertion, perhaps has palpitation, is depressed in spirits, and has feelings of numbness, stiffness, or even cramps in the limbs which may be tottery and feeble. Headache is not uncommon. There may be some form of catarrhal trouble, rarely diarrhoea, more often constipation and loss of appetite, or there may be occasional transient

flashes of fever, or what seems to be an attack of malarial fever. On some days the patient may feel comparatively well and fit for work, on others he is languid and lies up. He may notice that his ankles are slightly œdematous, and perhaps that his face is puffy.

With or without such a premonitory stage, symptoms of pronounced peripheral neuritis appear. During several days the symptoms are gradually intensified. Sometimes the patient, who had gone to bed the previous evening in apparently fair health, finds on waking next morning that he is hardly able to walk or even to stand; his shins and finger-tips are numb, his calf-muscles are tender, and he is conscious of various paræsthesiæ—such as burning and tingling—in feet, legs, and arms; the ankles and shins are swollen, and the hands and face puffy. Slowly or rapidly these symptoms become more marked, the œdema becomes general, the loss of power in the legs becomes almost complete, the arms weak, and the hand-grasp enfeebled. Palpitation and breathlessness, with substernal or epigastric distress, or it may be tenderness on pressure, recur in paroxysms at longer or shorter intervals, and the urine may be reduced to a few ounces. This condition may be further aggravated by cramps in the calf-muscles, which are now stiff, full and in many cases, though not in all, exquisitely tender when pressed against the bone. Usually the knee-jerks cannot be elicited after these symptoms have continued for a few days; in the early stages they may be increased and sometimes remain so for three weeks or, rarely, longer.

In this state of œdema, of partial paralysis, of muscular hyperæsthesia of cutaneous anæsthesia and paræsthesia, of breathlessness, of palpitation, of substernal and epigastric distress and oppression, the patient may remain for several days, weeks, or even for a month or two. His appetite may or may not be materially impaired; he finds, however, that indulgence in a full meal increases the epigastric distress, and so, as a rule, he eats somewhat sparingly. Digestion is fairly well performed and the bowels are regular, if anything inclined to constipation. The intellect is in no way disturbed, and, as a rule, there is no fever. He converses freely, and when not troubled with cramps, myalgic pains, palpitation, or dyspnoea, his state is by no means uncomfortable. After a variable period, during which he has ups and downs, he begins to pass urine more freely, and at the same time the œdema begins to subside. In severe cases, as the œdema disappears, it becomes manifest that the muscles of the legs and arms have undergone marked atrophy, sometimes to such an extent that the whilom muscular coëssion is reduced almost to a skeleton. He lies in his bed quite unable to move, or he may just be able to creep slowly about with the aid of a stick, or by clinging to the furniture and walking for support. He has no knee-jerk, he cannot stand with his eyes shut, his muscles are still very sensitive to pressure, the skin over the shins and the finger-tips is still numb, he buttons his clothes with difficulty, and he walks, if walk he can, like a patient with locomotor ataxia. In such cases there follows a long period of weeks or months during which the muscles are slowly restored, the hand-grasp gradually returns, the

power of locomotion slowly improves, last of all the knee-jerk reappears, but this may not be for very many months, perhaps for a year or longer. Such is a brief description of an uncomplicated attack of beriberi. There is a moderate amount of œdema, of anæsthesia, of muscular hyperæsthesia, and of paresis. There are occasional attacks of palpitation and of epigastric oppression. After a time, as the œdema subsides, evidence of extensive muscular atrophy is disclosed, and during a prolonged convalescence the wasted muscles are slowly restored.

But this description by no means applies to all cases. During an epidemic, and constantly in the endemic regions, every imaginable variety and modification of the essential symptoms, both as regards intensity and combination, is encountered. In one case the dropsy may be excessive, involving the trunk, limbs, and face, as in acute nephritis. Often in such a case the muscular paresis is really but slight, the principal hindrance to movement being the dropsy or the dyspnoea. Again, the brunt of the disease may fall on the muscles, which rapidly waste, the patient in a few weeks, with scarcely any accompanying œdema or but a mere trace over the tibiæ, may be rapidly reduced to a skeleton, paralysed in legs and arms, perhaps unable to move hands and feet or even fingers or toes. In a third case the more urgent and striking symptoms may be referable to implication of the pneumogastric and phrenic nerves: in such cardiac oppression, palpitation, dyspnoea, and substernal pain are the prominent features.

In some epidemics the vast majority of the cases are of a much milder type. The patient may be walking about. The œdema may be slight and limited to the lower extremities and confined to the anterior tibial region. The paresis is not sufficiently marked to produce any definite modification of the gait, and only shews itself objectively by impaired power. Cardiac symptoms may be limited to increased excitability of the cardiac action on exertion. This class of case appears to be more common now than formerly, and where it prevails the mortality from the disease is low—only 2 to 4 per cent. It must not be forgotten, however, that even in these cases exacerbations, with severe or even fatal cardiac complications, may occur quite suddenly and unexpectedly.

A rarer class comprises the most severe and fulminating cases, in which the pneumogastric is early and severely implicated. In these, cardiac oppression, palpitation, dyspnoea, and substernal pain are the prominent symptoms, and death may occur within a few hours of the first definite symptoms of the disease.

Between these main classes there are intermediate forms, and numerous classifications have been made according to the prominence of one or other symptom of the disease. One of the most variable features is the amount of œdema. Cases in which the parietic symptoms and muscular wasting are marked, and the œdema slight or transient, are often described as "dry," paralytic, or atrophic beriberi (*beriberi atrophicum*). In other instances dropsy is the prominent feature, and may be so pronounced as to simulate, as already mentioned, a case of acute

nephritis. These cases, with general cedema, are known as "wet" or "dropsical" beriberi (*beriberi hydrops*). In the later stages, when the dropsy has disappeared, such cases, since they now shew only the wasting, appear to be "dry" beriberi. The distinction between the two forms is artificial, and the terms are only to be used as descriptive and not as implying any real or essential difference. Rapidly fatal cases are often called "pernicious," whilst the milder forms in which all the signs are slight are sometimes described as "larval" or "rudimentary." "Chronic," "acute," "relapsing," or "recurring" are also used as descriptive terms in the classifications of the forms in which the disease appears. As with the expressions "wet" and "dry" beriberi, these terms indicate only phases of the same disease and not different diseases, and further, it must be remembered that the phases indicated are not sharply defined or separable one from another. Moreover, any one form may rapidly assume the characters of another form. The "wet" may change into the "dry" and vice versa. The chronic may acquire acute characters, and any form may rapidly develop pernicious symptoms.

Hamilton Wright has laid great stress on the essentially secondary nature of the nerve lesions responsible for the group of varying symptoms hitherto known as beriberi. He proposes to apply the term "post-beriberic residual paralysis or neuritis" to the usual clinical form of beriberi. The precursory disease, acute beriberi, according to him, comprises the supposed primary lesion, the "gastro-duodenitis" already mentioned, the formation of a toxin, and the action of this toxin on the nerves.

In proceeding with a somewhat more detailed account of the symptoms of beriberi, we note first, that there is no unquestionable evidence that any of the higher nerve-centres are ever attacked. The mental faculties are not markedly affected until perhaps the patient is dying, and with very rare exceptions there is no implication of the centres or nerves of sight, hearing, smell, or taste; nor, with the exception of wasting of the subcutaneous fat in certain cases, and some rare forms of erythematous eruptions in others, is there any evidence of the trophic lesions of the integuments that are usually associated with spinal disease. Bed sores, for example, occur in neglected cases only. Scheube records a case of what may have been a trophic joint-lesion; but such cases are extremely rare.

The lesions of beriberi are, all of them, such as we are accustomed to associate with secondary disease of the peripheral nervous system. Essentially they are of the same class, and many of them identical with those found in alcoholic, diphtheritic, and other forms of peripheral neuritis. Just as there is a tendency for each of these specific forms of neuritis to display a more or less characteristic grouping of symptoms peculiar to itself, and just as the poison of each of these diseases shews a predilection for particular groups of nerves, so beriberic neuritis, whilst it presents many features in common with the other forms of peripheral neuritis, presents special features more or less distinctive and peculiar to itself.

*Fever*—It is by no means established that fever is in any way an

feature in the history of beriberi, although it may be present time or another in the course of many of the cases. Occasionally supervenes on a malarial attack, or develops in the course of such ; at other times malarial fever may come on soon or long after beriberi is established. We have observed in cases of shewing these intercurrent attacks of fever, that the symptoms is were aggravated after the febrile bouts. In chronic cases no fever, or only as a coincidence ; often the temperature is normal, as it certainly is in all cyanotic or moribund cases.

*1a.*—The extreme liability to œdema is one of the peculiarities of beriberi neuritis ; comparatively rare in other forms of peripheral neuritis. œdema is an invariable feature in every well-marked attack of beriberi, either throughout or at one time or another. It always commences in the lower extremities, usually over the crest or inner surface of the thighs and about the ankles. It may be trifling in extent and confined to the lower regions ; on the other hand, it very often extends to the dorsa of the feet and, spreading upwards, gradually or quickly involves thighs, hips, and upper extremities, sometimes attaining an extreme degree. Moderate œdema, besides its invariable situation on the shins, is most marked about the flanks, the sacrum, the root of the neck, and the sternum. The degree of swelling may vary from day to day, and on the touch the œdema may feel firmer, and pit less readily than is usual in œdema associated with kidney disease. It also differs from renal and cardiac œdema inasmuch as it less frequently involves the genitals to a great extent. A peculiar form of localised œdema is sometimes met with, especially about the hands and arms ; a limited and sharply defined swelling of the integument, some four or five inches or more in diameter, is met with to a great extent. These localised swellings may develop in the course of a few hours, and disappear as suddenly. In some cases the œdema recedes by a few days the paresis and anæsthesia.

*1b.*—The development of a high degree of œdema always coincides with a diminution in the quantity and with a rise in the specific gravity of the urine. But the increased specific gravity is not proportionate to the diminished amount. The total solids are considerably below normal ; according to Scheube the chlorides are proportionally less diminished than the urea, especially when there are extensive serous effusions. When recovery takes place the urinary solids reappear in proportionately larger amounts. According to the same authority the excretion of phosphates is diminished. Bälz states that there is excess of indican, but indicanuria is not common in the tropics that no importance can be attached to this. Bälz, who has confirmed and extended these observations, sums up the result that the metabolism in beriberi is seriously diminished, and that the contributing organs, for example the liver, are diminished in their output. This, he points out, is in accordance with the fact that patients may complain of illness before the onset of marked œdema or of the involvement of the peripheral nerves. The urine may be scanty, reduced to a few ounces, and, in rare instances, there is complete sup-



pression. Although it occasionally contains albumin, this is an accidental and not a common feature. With active diuresis the œdema may entirely disappear in a day or two.

The *anæsthesia* varies in extent and degree within very wide limits. In the great majority of cases it is, like the œdema, an early manifestation, and, as a rule, is best marked and first detected over the front and inner aspect of the legs. In mild, and sometimes even in severe, cases it may not extend further. Usually, however, it creeps downwards over the dorsa and perhaps the soles of the feet, and upwards over the thighs, particularly on their inner and anterior surfaces, sparing the groins, perineum, and genitals. At an early stage it appears on the inner surface of the wrists, the backs of the hands, the fingers, finger tips, and palms, attacking them in the order stated. It may creep up the inner surface and back of the arm and involve the elbow. In many cases the skin over the chest and abdomen is also affected. Observers in Japan agree in describing a circle of anæsthesia around the mouth, and this has been noted elsewhere. The anæsthesia usually amounts merely to a blunting of sensibility and a delay in perception. The patient when touched feels as if a glove or piece of cloth were interposed. On being tested with an æsthesiometer the tactile areas are found to be enlarged. In rare cases the anæsthesia is complete. The perception of chemical, electrical, thermic, and painful stimuli is also diminished and delayed in the implicated areas. It is further to be noted that the patches of anæsthesia are not in conformity with the anatomical distribution of particular nerves; that, though usually symmetrical, the anæsthesia may in rare cases be limited to one side of the body; that in certain cases the finger-tips are the parts first or most involved; that the degree of anæsthesia varies from time to time in the same case; that it is most marked in atrophic beriberi; and that its degree and extent are not always proportional to the gravity of the case. *Hyperæsthesia* of the skin has been noted (Scheube); it is a very unusual condition. *Formicæ* — such as burning, pricking, formication, gnawing, darting pains, coldness, a feeling as if the affected part were swollen—may precede or accompany the other symptoms and prove very distressing.

*Paresis* to a greater or less extent always affects the muscles of the legs, and very often of the arms and hands; less frequently those of the trunk and face; very rarely those of the eye; and still more rarely the sterno-mastoid, the trapezius, and the muscles of mastication and deglutition. As a rule, the muscles supplied by the peroneal and anterior tibial nerves are first affected, then — and for the most part in the order mentioned — those of the calf, the extensors of the knee, the glutei, the flexors of the knee, the adductors and flexors of the thigh. Coincidentally with the appearance of paresis in the thigh, the muscles of the forearms and arms are attacked, including the extensors of the wrist and fingers, the supinator longus, the triceps, the flexors, and the small muscles of the hands and fingers. Then the abdominal muscles, the pectorals, the intercostals, the laryngeal muscles, and the diaphragm may all, one



come affected. The heart, too, as shewn by subjective y generally more or less implicated, and careful examination shewn that the muscular structure of this organ is power of locomotion is impaired in due relation to the s. In mild beriberi the patient can walk with or without a stick; the legs may feel a little weak and tottery, but arms are hardly affected, and the patient can, therefore, with a stick or in other ways. Generally the hand-er-power are decidedly impaired. In cases of greater ly is locomotion impossible, but practically all movement, except perhaps those of facial expression and the he eyes, and those associated with speech, mastication, respiration. Not only may the paralysis of the limbs be at of the trunk may be equally marked. In such a case y possible, owing to the paralysis of the laryngeal muscles ceed expiration; speech may be reduced to a whisper; s the feet fall into the equino-varus position in line with hands drop at the wrists. The patient may be entirely slightest movement, so that, atrophied and helpless, he back in bed, and is entirely dependent on others even for food in his mouth.

y writers allude to the *gait in beriberi* as quite characteristic features so special that it can be distinguished from forms of peripheral neuritis. In walking, the toes are sis of the flexors of the foot, to brush the ground when made to raise and advance the foot. This is extremely milder forms of the disease. In more severe cases, in sors of the foot as well as the flexors of the leg and involved, the heel can no longer be raised. Consequently still possible, degenerates into a sort of shuffle, and is forwards of one side of the body with the corresponding one side then of the other, than a walk. In bad cases re recourse to various contrivances to facilitate locomotion. As mentioned, some help themselves along by clinging to others—their legs well apart—lean with both hands on a stick which is thrust out in front of them, and towards which they are leaning whilst leaning their weight on it; some retaining considerable power in their arms, but completely paralysed in their legs and quite unable to stand, by placing their hands behind them and sitting half up, contrive to push themselves forward.

Some patients can stand for any length of time with eyes closed, the feet closely approximated, and, like an ataxic patient, could fall if unsupported. Doubtless imperfect perception as well as muscular weakness, play some part in this; very often an additional element of inco-ordination superadded. The arms exhibit similar muscular incapacity, though, as a

rule, in a relatively slighter degree. Thus the weakening of the finger muscles, together with the blunting of sensation in the finger-tips and slight inco-ordination, may render buttoning and unbuttoning of the clothes difficult or even impossible, while writing and other delicate movements may be out of the question. When the abdominal and perineal muscles are seriously implicated, any attempt to cough results in the unsupported diaphragm being forced down and projection of the anterior abdominal wall, the perineum being manifestly bulged downwards at the same time. In such circumstances it is obvious that defecation and micturition may be seriously interfered with, although the sphincters are not affected. During recovery there is sometimes a spastic-like movement of the muscles—particularly of the legs. Occasionally, as a sequel of the muscular degeneration, permanent weakening of the foot flexors occurs; and, as a result of a consequent contraction of the gastrocnemii, even organic and permanent retraction of the heels may result.

*Hyperæsthesia* of the affected muscles is always present, sometimes in a very marked degree, so that squeezing or pressure against underlying bone is painful, and may be so severe as to make the patient cry out, or be quite unbearable. This symptom, which is most easily elicited in the gastrocnemii, the thenar muscles, and in those of the thigh and forearm, is of great practical use in diagnosis.

*Cramps* sometimes occur, especially at the outset, and may come on spontaneously at any time, but are most frequent during the night or on movement. In rare instances the muscles may be thrown into a state of *tetanic contraction*; a *convulsive form* of beriberi has been described, and *opisthotonos* has also been observed.

*Atrophy*, as a rule, rapidly supervenes in the paretic, hyperæsthetic, and flaccid muscles, and is generally very evident on the subsidence of the cedema in hydropic beriberi, and almost from the outset in the atrophic form. The wasting is often extreme, and restoration is but slowly effected, many months elapsing before the process is complete. Occasionally one or more muscles are permanently atrophied.

*Swelling of the muscles* has sometimes been observed; in these cases the bellies and outlines of the muscles are prominent, and the patient though excessively feeble, may have the appearance of an athlete. This condition appears, in most instances, to depend on cedema of the connective tissue of the muscles; in a few cases, possibly on vascular congestion. Circumscribed swellings are not infrequent in some of the muscles, particularly in the inner belly of the gastrocnemii, but their exact nature has not been determined.

*The reaction of degeneration* can be demonstrated throughout the disease; according to Pekelharing and Winkler changes in the electrical reactions can be found even before the onset of any other symptoms of impending beriberi. *Tenderness of superficial nerve-trunks* can sometimes be elicited. The *knee-jerk* is almost always altered; in early cases it is frequently exaggerated, but ultimately, with rare exceptions, it is

. The *superficial reflexes* are usually preserved, but in high degrees of phic beriberi they are also for a time abolished.

Inflammatory swelling of the *lymphatic glands* of the groin, according Scheube and others, occasionally occurs. Bentley states that *con-  
ion of the fauces*, sometimes very intense, is almost invariably present; some epidemics in Malaya this condition was the rule, in others it rarely, if ever, seen. *Paralysis of the soft palate* has been observed.

*The blood* is said to be defective in alkalinity; but this statement, many others regarding the chemical alteration in the blood, must be ived with caution. Many careful and reliable estimations of the puscular richness and of the hæmoglobin of the blood have been le; the opinion of all the later observers is that, although beriberi y be accompanied by anæmia, in a large proportion of the cases the puscular richness of the blood is perfectly normal. As a cause of emia the poison of beriberi is much weaker than that of malaria or en of rheumatism.

*The pulse*, usually accelerated, is exceedingly sensitive to exertion, n to change of posture. Scheube remarks that in bad cases slowing the pulse may occur before death, and gives two examples, in one of ich the pulse fell in five days from 120 to 54, in the other from 104 20. The finger and sphygmograph shew low arterial blood-pressure d diminished cardiac power.

*Cardiac murmurs*, usually systolic, are present in a large proportion cases; occasionally there is accentuation, very often reduplication, of sounds. Pulsations in the veins of the neck is also common, and probably the result of tricuspid insufficiency from dilatation of the ht ventricle. Epigastric pulsation is common. *Palpitation* is en the most troublesome of all the symptoms. It is provoked exercise, by eating, sometimes even by rising up in bed, and asionally is persistent. It is usually worst at night or in the morning, l is often accompanied by intense dyspnœa. Cardiac oppression is en a very urgent subjective phenomenon, and may occur independently palpitation. Frequently also there is a feeling of fulness amounting pain in the region of the stomach; this is possibly connected with state of the heart or with some condition of the diaphragm. Dilata- of the heart to the right, as shewn by percussion and diffusion of pulse, is often very evident, and may be associated with extreme pnœa, cyanosis, and other indications of failing cardiac power.

*Vomiting*, unconnected with digestion, and *aphonia* indicate implica- of the pneumogastric, and should always, particularly the former ptom, be regarded as of grave import. *Diaphragmatic and inter-  
al paralysis* is not uncommon.

*Serous effusion* into the pericardium is by no means rare, but is lom so extensive as to be in itself a source of danger. Hydrothorax occurs, but it is very seldom that it is sufficiently large to give rise grave symptoms; in fact this result is even rarer than in the case of tropericardium. Ascites, to a notable extent, is rarer than either.

*Edema of the lungs* is very apt to occur in the hydropic form of beriberi, and is frequently the immediate cause of death. Its onset is shewn by increasing dyspnoea accompanied by cough and frothy expectoration, and, if the patient live long enough, by fine moist crepitations.

*Digestion* is usually feeble and the stomach dilated. A full meal may cause distress from pressure of the distended stomach on the weakened heart; it is probably for this reason that rice and other bulky foods are ill-borne in beriberi. Diarrhoea sometimes occurs at the outset, but more commonly there is constipation; in the later stage of hydropic beriberi constipation is often a marked feature.

*Mode of Death in Beriberi.* In the progress of a case of beriberi, no matter how trifling it may appear, symptoms indicating great danger may set in suddenly and at any moment. This may be within a day or two of the commencement of the attack, or it may not be for one, two, or more months. The threatening symptoms, for the most part, appear to depend on extension of disease to the pneumogastric or phrenic nerves, on the occurrence of oedema of the lungs, on the development of extensive hydropericardium, or, it may be, on a combination of two or more of these conditions. In the great majority of cases the principal factor in the fatal event is the parietic condition of the heart; when this is marked, a very slight increase of other unfavourable conditions may turn the scale and bring about fatal over-distension. In rare cases death may occur from sudden syncope; usually, however it is the result of the slower process of dilatation. As this advances, the patient is seized from time to time with agonising dyspnoea; he sits up in bed and struggles for breath, his face is cyanosed, his eyeballs start out of his head, and his cervical vessels pulsate visibly. The heart's action is excited, labouring, and at the same time inefficient; the impulse is diffused, and is communicated to the epigastrium. Percussion shews that the right auricle and ventricle are dilated, and loud murmurs indicate that the valves are incompetent. Concurrently with this the pulse becomes small, feeble, and flickering; the extremities become blue and cold, the temperature falls, cyanosis deepens, the patient becomes unconscious, and after a short time dies. If he recover from one such attack, another and more severe one will probably supervene in a short time; and sooner or later one of these attacks proves fatal.

**Mortality.** The published returns from various places shew an enormous variation in the mortality. This variation is due in part to the frequency of different complications, dysentery and the like. In beriberi uncomplicated by other disease there is still great variation, in some outbreaks it has been as high as 40 per cent. The prison returns are the most reliable guide to the case mortality in uncomplicated beriberi. In the Malay Peninsula this seems to be less now than formerly, amounting only to about 2 to 6 per cent; while in the earlier records 10 to 15 per cent, or even more, was not uncommon. The general tendency in all places has been to a similar reduction in the case mortality.

gh the death-rate may be high at the commencement of epidemic ks, it becomes much lower later on. Hospital statistics are a value as to the true mortality, since they refer to cases of , many of which are complicated by other diseases, and it then is a matter of personal judgment whether the deaths are returned ne heading of beriberi or of the associated disease.

he Japanese Navy the case-mortality in beriberi was given as (1878-1884), whilst in Christmas Island in 1905 it was less er cent. Speaking generally, an outbreak with a mortality of 5 per cent is exceptionally low, and one over 10 per cent nally high. The more numerous the markedly hydropic forms, ter the mortality.

els.—As can be readily understood, serious deformity may om imperfect restoration of muscles after an attack of beriberi. Cl talipes equinus is not uncommon in countries where beriberi is d in many instances is probably consequent on this disease. On and hypertrophy of the heart, permanent cardiac murmurs, or feebleness of legs and arms, circumscribed anæsthetic patches skin, and liability to œdema of the feet and ankles, have also umerated among the sequels.

the great majority of cases complete recovery occurs. Even the s become normal. This may be delayed for years, but out of even cases recorded by Travers, they were present in forty-one in a less after the attack of beriberi.

apses and recrudescences are frequent. Various estimates have ade as to their frequency. In a country or institution where i is endemic a large proportion of persons admitted to hospital s disease give a history of a previous attack, and as long as ease remains endemic in an institution "relapsed" cases are t. A large proportion of these cases are probably reinfections sentially fresh attacks. In hospitals in England, such as the 's Hospitals in London, where the conditions are not favourable ection, cases admitted in various stages run a fairly steady course ly slight fluctuations, and serious recrudescences do not take place convalence. In the Kwala Lumpur Prison, Malay States, a period of seven months, in which no cases originated in, or were d to, the gaol, no relapses took place, though there was a large of prisoners in the gaol who had had beriberi during the previous ars. This was in marked contrast with the previous six months, ome 107 fresh cases originated in the same prison, and no less than lapses occurred. It is impossible, therefore, to avoid the conclu at many of the so-called relapses are in reality fresh attacks, due same conditions that caused the original attacks. True relapses r, and may be repeated even when such conditions are not , but they are not common. Thus in the Taiping Prison, in the between September 1897 and June 1899, there were no admis- ith beriberi, and no fresh cases occurred in the prison, but one man

who had had the disease previously suffered three relapses, in March, July, and August 1898 respectively.

It appears that persons who have had beriberi previously are not liable to acquire the disease again, rather than that true relapses are frequent. In persons who have had severe attacks with incomplete recovery, slight increase in the residual symptoms is not uncommon. Slight causes, such as overwork, exposure to wet and cold, or intercurrent disease, may result in marked increase of the existing symptoms just as in other forms of peripheral neuritis.

**Diagnosis.**—An epidemic of beriberi presents no difficulties. The distribution of the nerve-lesions, the absence of cutaneous eruptions and of the other characteristic symptoms of arsenical poisoning, distinguish the disease from *arsenical neuritis*, the only other known form of peripheral neuritis that would affect at once a large number of people. Epidemic peripheral neuritis probably means beriberi. Isolated cases present more difficulty. The diagnosis must be made from all other forms of peripheral neuritis, and in some cases this may be impossible. In the early stage of the hydropic form, and very rarely during the entire course of the attack, it sometimes happens that distinct symptoms of peripheral neuritis do not declare themselves; for a time there may be no marked anæsthesia of the skin, no muscular hyperæsthesia, the knee-jerks may be present or even exaggerated, and œdema may be the only manifestation. But in the presence of an epidemic of beriberi, the rapid development of œdema, without albuminuria or other manifest cause, points to this disease. Any doubt is usually dispelled in a very few days by the appearance of the usual signs of peripheral neuritis.

The occurrence of *malarial neuritis* at all resembling beriberi is very rare, and in the cases that appear to be of this nature there are usually mental disturbances, especially loss of memory. In *alcoholic neuritis* œdema is not nearly so common nor so extensive as in beriberi; this consideration, together with the tremor, gastric catarrh, mental condition and, above all, the history of drinking, should lead to a correct diagnosis. It is highly probable that in beriberi districts cases of double, or even triple nerve-poisoning from beriberi, malaria, and alcohol occasionally occur.

In some countries *post-dysenteric neuritis* is not very uncommon: it resembles beriberi in the presence of firm, hard œdema, but the changes are limited to the lower extremities, the upper extremities and the heart not being affected. These manifestations follow an attack of dysentery so closely that their connexion with that disease will at once be suspected.

A paralytic affection called *lathyrism*, resulting from the use of a dal prepared from a lentil—*Lathyrus sativus*—prevails extensively in Upper and Central India, especially near Allahabad and in Upper Sind: it is also found in Algeria. From beriberi it is easily diagnosed, as it is a spastic paralysis, evidently of spinal origin, affecting the lower limbs only, and associated from the outset with bladder-symptoms, as well as



with exaggerated knee-jerks. Dropsy, cardiac symptoms, anæsthesia, and disturbance of the electrical reaction of the muscles are absent (vide "Lathyrism," Vol. II. pt. i. p. 898).

The œdema, muscular pains, and tenderness of *trichinosis* might suggest beriberi, more particularly as both diseases are apt to occur in limited epidemics. But the seat of the pains in trichinosis, principally in the muscles of the trunk, head, and neck; the violent gastro-intestinal disturbance preceding the muscular pains; the well-marked fever; the early œdema under the eyes and in the face; the absence of true paresis; the implication of the muscles of the eyes, face, and neck; the absence of œdema on the front of the shins, of anæsthesia, of heart trouble; and the circumstances in which the malady occurs, should make diagnosis easy enough.

Besides the evidence afforded by the microscopical examination of the stools, *ankylostomiasis* may be distinguished from beriberi by the intense anæmia, the gastric symptoms, and the complete absence of any evidence of neuritis.

*Malingering* and *hysterical mimesis* are readily detected by an examination of the knee-jerks, by the electrical reaction of the muscles, and by the absence of œdema, cardiac irregularities and murmurs.

It should, however, be noted that groups of cases of peripheral neuritis occasionally occur which in certain important points, such as persistence of knee-jerks, differ from beriberi as ordinarily met with. The same may be said of the other prominent symptom of beriberi, namely, œdema. It is possible that such outbreaks are a distinct disease, and that other forms of peripheral neuritis of unknown origin are sometimes mistaken for beriberi.

**Treatment.**—No specific treatment is known. Since repeated re-infection or absorption of the poison appears to be possible, the patient should be removed to a part of the building where no new cases originate, or, better, to some place at a distance where beriberi is not endemic.

While the symptoms are acute or progressive the patient must be kept in bed, and not allowed to sit up or make the slightest exertion. While the diet should be liberal and varied, bulky foods, such as rice, should be avoided, on account of the danger resulting from gastric dilatation and its effect on cardiac action. For the same reason food and drink should be given in small quantities at a time, though the total amount may be liberal. Constipation should be obviated; benefit accrues from the administration of small but frequent doses of salines, such as the sulphates of magnesia or soda. In the presence of failing heart, cardiac tonics, such as strychnine and digitalis, should be administered. Cardiac failure and over-distension of the right ventricle are the two main dangers, and grave symptoms resulting from this condition may appear suddenly, even in cases apparently progressing favourably. In such cases the symptoms are urgent, and full doses of nitrite of amyl, 5 minims—by inhalation—or

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nitroglycerin,  $\frac{1}{100}$ th of a grain, or liquor trinitrini, 1 minim as a hypodermic injection, should be at once administered, and repeated as required. An energetic cathartic, such as croton oil or castor oil, should also be given. As these cardiac crises occur without warning, all the necessary appliances should be kept ready by the bedside, and the attendant fully instructed how to treat the attack. When death appears to be imminent, venesection will give relief and should, therefore, be carried out, as it allows time for other measures to take effect; it, however, has usually to be repeated. Hydrothorax or hydropericardium, if excessive, must be relieved by aspiration. When the paralysis is marked, great care should be exercised by means of passive movements to prevent contractures and fixation of the joints. The bed-clothes should be supported by a cradle as their pressure maintains the position of foot-drop. Splints—preferably anterior splints—may be used to prevent the condition becoming permanent. Bed-sores only occur as the result of gross neglect.

When the acute symptoms have subsided, and danger of cardiac failure has passed, graduated exercises are of great value. Massage and faradisation should be employed in such cases when the muscular tenderness has materially decreased. The diet should be liberal. Change of scene and residence expedites complete recovery. In view of the liability to second and third attacks, return to a country or place where beriberi occurs should, when possible, be prohibited.

**Prevention of Epidemics.**—Provision of dry, well-ventilated quarters, whether in prisons, ships, or coolie-lines, appears to exercise some deterrent effect. A liberal dietary also plays some part in preventing and checking an epidemic.

Overcrowding must be avoided. In view of the manner in which the disease spreads in an institution, every precaution must be taken to prevent any possibility of infection by clothes, blankets, bedding, sleeping bunk or cells, as it appears to be by these rather than by immediate contact that the disease is spread. The disinfection thus employed should ensure the destruction of vermin. The earliest stages of the disease appear to be the most infective; if the disease be infective—and it does—comers should be kept separate, as far as possible, till it is known whether they are the subjects of beriberi or not.

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## EPIDEMIC DROPSY

By Col. KENNETH MACLEOD, I.M.S., M.D., LL.D.

**History.**—In the year 1877 an outbreak of a disease, the principal feature of which was dropsy, occurred in the southern suburbs of Calcutta. It continued to prevail during the cold season of 1877-78, disappeared in the hot weather, recurred over a wider area in the cold months of 1878-79, subsided again in the hot weather, broke out a third time over a more extensive area of the town and suburbs in the cold season of 1879-80, and vanished in the hot weather of 1880. The disease appeared to a limited extent in Calcutta in the hot season of 1881. The new ground invaded in each recrudescence was contiguous to that which had been previously occupied, but isolated offshoots also occurred: the larger and more distant of these were a well-defined outbreak in the hill station of Shillong, in the Khasia Hills, Assam, in the winter of 1878-79; and a somewhat severe prevalence among natives inhabiting the city of Dacca in Eastern Bengal, and among coolies employed in the tea-gardens of South Sylhet during the same time. A similar epidemic broke out in the island of Mauritius in November 1878, and continued to prevail extensively until April 1879, when it died out. Labourers from the tea-gardens of Assam and Sylhet, and for the sugar-plantations of Mauritius, pass through Calcutta; the latter embark at the place where the disease first made its appearance.

This remarkable epidemic of dropsy was very carefully observed in each locality, and its phenomena—clinical and epidemiological—have been minutely recorded by Drs. Davidson, O'Brien, Crombie, and others. At first it was thought to be a manifestation of beriberi, in most cases of





Pleasant sensations often preceded and accompanied the development of the anasarca, and in a considerable proportion of cases the surface became erythematous or affected with an urticarial, scarlatinal, or billous rash. Vesicles and petechial and purpuric spots were also observed. These rashes appeared in the earlier stages of the attack; pruritus, desquamation, excoriation, and ulcers were occasionally observed. The deep-seated pains probably depended on the pyrexia, and subsided within the first fortnight. The condition of the urine varied as regards colour, quantity, specific gravity, and frequency of discharge.

Tube-casts or albumin were found. In severe cases respiration and circulation were much disturbed. The cough, dyspnoea, and orthopnoea observed in some cases were evidently due to oedema or congestion of the lungs, and effusion into the cavities of the chest—conditions which occasionally caused sudden death. Anæmia was a prominent and constant feature of the disease, which in Mauritius received the name of “acute anæmic dropsy.” The red corpuscles were diminished in number, the leucocytes increased, and an unusual amount of granular and molecular material was observed in the blood. The disease in severe cases produced considerable prostration and emaciation. No enlargement of the spleen was noticed, but in some cases, in which cardiac and pulmonary complications existed, the liver was found to be tender and its area of dulness extended. Neither anæsthesia nor paralysis was observed, though these symptoms were carefully looked for both in India and Mauritius. The duration and severity of the disease varied considerably. From three weeks to three months may be stated as the limits of duration. Debility, anæmia, and persisting oedema of the legs were the only sequels observed. The case-mortality varied between 2 and 8 per cent. Some Calcutta returns gave higher figures, but they probably included an excess of fatal cases. Death was caused mainly by pulmonary and cardiac complications, and in some cases was sudden and unexpected. Post-mortem examination revealed effusions and congestions. The subcutaneous fusion was in some cases hard and sanious. Punctate extravasations of the skin and serous surfaces were observed; congestions of stomach and intestines, of the liver and mesenteric glands, and cloudy swelling of the renal epithelium, were also noted. No bacteriological investigations were made either in India or Mauritius in the outbreak of 1877-8. The descriptions of the phenomena of the disease more recently recorded by Drs. Rogers and Cobb agree very closely with the foregoing.

**Epidemiology.**—The various geographical and meteorological conditions under which the disease prevailed indicated that place and season had no important influence in the causation of this malady. The curious Calcutta experience of three outbreaks, with two intervening periods of latency, shewed that the conditions existing in the cold season were more favourable to its development and spread than those obtaining during the hot weather and rains. It was also in the cold season that the disease prevailed in Shillong, Dacca, and South Sylhet; but in Mauritius neither temperature nor humidity, rain nor drought, elevation nor soil, seemed to

affect the course of the epidemic. The element of malaria may also be eliminated. Nor did food or water, shelter or clothing, cleanliness, comfort, general salubrity or the reverse, appear to govern the origin and spread of the disease; though unfavourable personal and hygienic conditions probably affected the issue in individual cases, and aggravated the severity of seizures and the general mortality. In the years 1876 and 1877 Southern India was visited by a terrible famine, and scarcity and dearness of food prevailed in Bengal at the time when the disease appeared in Calcutta. Numbers of starving people flocked into that city from the famine tracts, and fever, cholera, and small-pox were more than usually rife and deadly; but this dropsical disease was by no means confined to the impoverished and sickly; and in other localities which it visited such conditions were absent. Natives of India were the chief or only victims of the malady, which appeared and spread, in the first instance, among the members of a particular section of the native community, and then extended to other sections more or less associated with them. In Calcutta, Mohammedan tailors and boatmen were first attacked; and subsequently native villagers of all races and castes living in the same or adjoining hamlets. A few Eurasians and Armenians suffered, but no European. In Shillong, Bengalis were primarily and principally the sufferers; later a few hillmen and Goorkhas took the disease. In Dacca the disease prevailed among natives only, and in Sylhet among the garden coolies exclusively. In Mauritius it broke out among Indian labourers, and prevailed most among those imported from Calcutta. The general population subsequently suffered, though to a smaller extent. Adults were the most numerous victims, and males were attacked in larger proportion than females; but children were not exempt, and among these sex-proportion was more equal. The outbreaks in all places presented the character of an epidemic rather than an endemic. Neither before nor after the outbreak did any disease presenting similar symptoms exist endemically or appear sporadically in any of the places visited.

There is some ground for belief that the disease was originally imported from the Madras famine tracts. Dr. Rammay Ray, who had been on famine-duty, had treated 500 cases of a dropsical disease in the famine country—which was called beriberi; and on his return to Calcutta he identified the malady which he found prevalent there with that which he had seen in Madras. Calcutta was undoubtedly the centre from which the disease was carried to other places—to Dacca, Sylhet, Shillong, and Mauritius. The spread of the disease was accomplished by human agency and intercourse. The manner in which it grew in households and communities proved its communicability, and numerous instances of grouping and importation were recorded. Its diffusibility was, however, by no means keen nor its incidence strong. In Mauritius, where the conditions of prevalence seemed to be more favourable, only about one-tenth of the persons exposed to the risk of contracting it suffered, and in other places the proportion of victims was less and the margin of immunity greater.

**Diagnosis.** The only disease with which epidemic dropsy is likely to be confounded is beriberi, but on comparing the clinical and epidemiological characters of the two diseases a radical distinction between them becomes apparent; there ought in future to be no difficulty in discriminating the one from the other. Beriberi is a peripheral neuritis of which dropsy is not an invariable accompaniment; epidemic dropsy partakes more of the nature of an exanthem, the dropsy is a constant feature, and the nervous phenomena characteristic of beriberi are absent. Epidemic dropsy is a febrile disease, in beriberi fever is either masked or absent. The congestions and eruptions observed in epidemic dropsy are rare or absent in beriberi. This is also true of the gastro intestinal disorder so frequently seen in the former. Beriberi is a more severe, protracted, and fatal disease, it is also an endemic rather than an epidemic disease, the opposite being true of epidemic dropsy, the former has also more definite geographical limits than the latter, and the circumstances of climate and season favouring the development and spread of the two diseases are different, if not opposite—beriberi flourishing under warmth and damp, epidemic dropsy under cold and dryness. Beriberi seems to be a disease of soil and habitation, epidemic dropsy of families or communities—the propagation of the latter being more manifestly due to association and intercourse than that of the former, which seems to depend rather on common exposure to morbid conditions. The diffusibility of epidemic dropsy, though not very active, exceeds that of beriberi, which requires a greater degree of concentration of its poison in circumstances of overcrowding, filth, and deficient ventilation to render it active and effective. The absence of endemic prevalence of beriberi in the localities where the dropsical disease prevailed negatives the idea that the latter was an accidental epidemic manifestation of a malady of usually endemic habit.

**Treatment.**—Such measures of segregation and disinfection as are ordinarily employed in the case of the exanthems are indicated in the management of an epidemic such as this. No special system or plan of medical treatment or regimen was employed in these outbreaks, symptoms and complications being met by the ordinary principles and methods of rational medicine.

KENNETH MACLEOD

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## LEPROSY

By PHINEAS S. ABRAHAM, M.A., M.D., B.Sc.

DERIVATION.—Λεπρός, scaly.

SYNONYMS.—English: *Elephantiasis Græcorum*, *Lepra*, *Satyriasis*, "Great Disease," "Mycele Ail"; and in the West Indies, "Joint Evil," *Cocobay*, "Bumpy Sick," and "Scrophula." French: *La lèpre*, *Ludrerie*. German: *Aussatz*, *Lepra*. Italian: *Lebbra*, *lepra*. Spanish: *Mal de San Lazaro*, *Lepra*. Norwegian: *Spedalske*, *Spedalskhed*, *Likpra*. Swedish: *Spetilskan*. Icelandic: *Likprær*, *Holdsvreiki*. Finnish: *Spetilskan*. Russian: *Prokaza*, *Crimka*, *Opasnaya*, *Kilka*, *Prypudek*, *Crimean disease*. Greek: *Elephantiasis*, *Elephas*, *Elephantos*, *Satyr*, *Satyriasis*, *Leontia*, *Leontiasis*, *Nousos Phoinike*. Sanskrit: *Kusta*. Arab: *Baras*, *Dsjudam*, *Jasam*, *Da el ased*. Indian: *Sunbahiri*, *Korh*, *Maha-korh*, *Rakt-korh*, *Pes*, *Charak*, *Ructa Kusta*, *Koostum coostam-gum*, *Kol*, *Patgurme*, *Raght-pite*. Chinese: *Ma Fung*, *Tu ma fong*, *Li fong*. Japanese: *Shinshi*. Maori: *Ngerengere*, *Puhipuhi*, *Tuckema*. Hawaiian: *Ma'i Pake*, *Lepera*.

**Short Description.**—A bacillary disease, apparently peculiar to man, of slow incubation and chronic course; manifesting itself in most cases by cutaneous pigmentary changes, and always by the formation of characteristic neoplasms, particularly in the skin, mucous membranes, and nerves, which give rise on the one hand to obvious thickenings and nodosities, on the other to alterations in sensation (analgesia, anæsthesia), and to tissue degenerations, ulcerations, and progressive contractions and mutilations of the extremities.

**History.**—*Leprosy in Ancient Times.*—There is reason to believe that leprosy was a known disease many centuries before our era. The earliest reference to it appears to be in a papyrus discovered at Memphis—the "Ebers papyrus"—which was written during the reign of Rameses II. 1348-1281 B.C. Prescriptions for the cure of a disease called *Uchetu*, characterised by nodosities and pain, and most probably leprosy, are therein contained, and these date, if we accept the authority of Brugsch, from the period of Hesepti of the legendary first dynasty (4600 B.C.), that is, from a time long antecedent to the Mosaic Exodus. *Uchetu*, in Prof. Macalister's opinion, is probably the same disease as the *κρόμας* of Hippocrates.

An early Biblical notice of "tsaraath" occurs in Leviticus, chap. xiii., in which, however, the description seems to apply better to certain other affections than to "leprosy" as at present understood. In other passages in the Bible also, as in Exodus, chap. iv., we read of "leprous as snow."

Now, the enactments in Leviticus refer chiefly to questions of diagnosis

in the first stages of the disease, and whether the sufferers should be made outcasts or not; in this connexion we must remember that some of the early cutaneous phenomena of leprosy, as will be seen later, may imitate to some extent the characteristic lesions of such diseases as leucoderma, morphea, etc. It may be assumed, however, from many allusions in the Bible and other ancient writings, that true leprosy existed largely among the early Jews; although it was doubtless then, as it is now, by inexperienced observers, confounded with other chronic and severe maladies of the skin, like leucoderma, the syphilides, the tuberculides, warts, malignant growths, and even scabies, eczema, psoriasis, and several other obstinate cutaneous affections.

Leprosy seems to have been also prevalent in ancient days in Persia, where, before the time of Herodotus (Herod. i. 136), there were stringent laws for the expulsion of lepers from the towns. Atossa, wife of Artaxerxes II., was said to have been affected with the disease.

In India, leprosy, under the name of "Kushta," was first described by Atreya, who is quoted in the *Rig Veda Sanhita*, a work dating from about 1400 B.C.

The disease was first recorded in Japan about 1250 B.C.; but in China it does not seem to be alluded to in the earliest accessible documents. It is believed, however, that it was first noticed in that country one or two centuries before Christ.

It has been surmised that Egypt was really the birthplace of leprosy, that the Jews took it thence, and that by the commerce and wars of the Egyptians it was carried to the far East. The evidence in support of these opinions is very scanty.

In all the countries mentioned above, leprosy has continued to exist until the present day as an endemic disease.

Leprosy is first mentioned in Europe by Aristotle about the year 45 B.C., under the term "Satyria." Hippocrates, indeed, at an earlier date, speaks of λεπρά, but the description given doubtless refers to the disease we now call psoriasis; and he also refers to the "Phœnician disease" as the cause of the λευκαί or white affections. In the third century before Christ leprosy had probably become more common in Greece; and at about that time and subsequently it was known chiefly by the names "Elephantiasis" (Aretæus, Galen, Celsus) and "Leoniasis" (Aretæus). Aretæus, in the first century A.D., gives an excellent description of it.

The disease is believed to have spread in early times from Greece to the neighbouring countries of South-Eastern Europe; and it first attracted attention in Italy during the first century B.C., shortly after the return of the Pompeian army from the East.

*Leprosy in the Middle Ages.*—It is quite possible that leprosy may have been carried by the Romans to all parts of their vast empire, through their relations on the one hand with Asia and Africa, and on the other with various countries of West and North Europe; at any rate it gradually increased in these countries to such an extent that a few

centuries later it was deemed necessary to establish leper asylums—as in Spain, Germany, France, England and elsewhere.

Various expeditions and migrations, subsequent to the fall of Rome, no doubt largely influenced the distribution and exacerbation of leprosy in Europe during the early Middle Ages; the advent of the Moors and the goings and comings of the Crusaders may have had such a direct or indirect effect. The diffusion may to some extent be followed by noting the dates of legislation on the subject, for laws dealing with lepers were enacted in Lombardy in the seventh century A.D., rather later in France—by Charlemagne in 789, and by Noel Iha, King of Wales, in 950.

The earliest leper asylums appear to have been established in the eighth century; but the greater number of these institutions, which were rather of the nature of religious houses than of hospitals in the modern sense of the term, date their foundation from the eleventh to the thirteenth century. In England the first was founded at Canterbury in 1096; and from that time until the year 1472, when the last was established at Highgate, some 112 such institutions arose in different parts of the country. One of the earliest was in St. Giles', London, and another occupied the site of the present Palace of St. James's.

From England leprosy gradually spread to Scotland, and ultimately to the Northern Isles, where indeed it lingered longest. Robert Bruce died of leprosy in 1329. Towards the end of the fourteenth century the disease was rapidly declining in England, and a Commission which was appointed in 1470 reported that very few lepers were left in the lazaretto-houses. Leprosy had practically disappeared from England before the accession of Henry the Eighth, but not from Scotland until much later. The last indigenous leper was seen in the Shetland Isles in 1798, and a case occurred in Edinburgh in 1809.

In France no less than 2000 lazarettos are said to have existed during the thirteenth century, and there were many others in the remaining civilised parts of Europe. Unquestionably a considerable number of the unfortunate inmates of the lazaretto-houses of the Middle Ages were sufferers from syphilis and various chronic diseases of the skin, for we know that in the beginning of the sixteenth century, when physicians were better acquainted with such diseases, and especially with the diagnostic signs of syphilis, a revision was made of the lazaretto-houses of France and Italy, and it was then found that in many of them the majority of the inmates were not suffering from leprosy. Taking all the facts into consideration, it must nevertheless be admitted that true leprosy was undoubtedly widely prevalent over the greater part of Europe during the Middle Ages, that it gradually diminished in most of the countries from the fourteenth century onwards, and that it has remained as an endemic disease in certain districts only. The descriptions of the mediæval writers shew that the disease was the same then as now.

**Geographical Distribution.**—At the present time leprosy is widely but unequally distributed over the earth's surface. It occurs as an



endemic disease in many places in the tropics, in the temperate zones, and even so far north as the Arctic Circle.

In Europe the principal centres are—(1) in Western Norway, near Bergen, along the borders of the Norde and Søndre Fiords; in the neighbourhood of Molde and Trondhjem, and as far north as Hammerfest and the Lofoden Islands; (2) North Russia, the countries and provinces on the borders of the Baltic (Finland, Lirland, Courland, etc.); (3) Southern Russia (the province of Kherson, Tauride, the Don Cossack, Cuban and Tersk, Stavropol, Astrakhan, and Ural Cossack Districts); (4) Greece (Acarmania, Laconia, Messenia, and the Grecian Archipelago); (5) Turkey (Thessaly, Macedonia, Rumelia); (6) the larger Mediterranean Islands (Crete, Cyprus, Sicily, etc.); (7) Spain (Alicante, Malaga, Granada and Seville); and (8) Portugal (Beira, Estremadura, Algarve). Leprosy is prevalent in Iceland, and until recently increasing. Bjarni hedinsson states that the cases are now about 130.

A limited number of indigenous cases are, moreover, still to be found in several other European countries, for example, in Sweden, Italy (the Riviera, Naples), Rumania, Hungary, France (the Riviera, Nice, about the delta of the Rhone, and possibly Brittany) and in North East Prussia.

The European leper asylums now established are situated at Bergen<sup>1</sup> and Trondhjem (the Norwegian asylums now contain together about 250 inmates), Reikiavik (Iceland), Dorpat (also at Oesel, Rigi, and Lirland in the Baltic provinces), Constantinople, Cyprus, San Remo, Alicante, and Lisbon.

In other places where leprosy is not endemic, cases are occasionally met with, as in London, Paris, Vienna, Berlin, Rome, etc., but such patients have invariably acquired their disease as natives or sojourners in some other country in which it persists. In 1897 I estimated that there had been since 1885 from 80 to 100 lepers in Great Britain and Ireland—I could find definite records of 56 cases. About 30 have been under my own observation within the last 18 years in London. There is, however, no reason to suppose that leprosy is increasing in this country. With two doubtful exceptions all the cases had lived in leprosy countries. Mr. Pernet has lately estimated that there are probably not more than 40 at the present time in the British Isles.

In Asia leprosy is as widely prevalent now as in ancient times. It occurs in Asia Minor, in Palestine (with an asylum at Jerusalem with about fifty inmates), the mountainous districts of Syria, Kurdistan, Persia, Turkestan, Arabia (especially at Muscat), in Siberia (where in the Yakutsk district there are probably about 100 lepers), Kamtschatka, Japan, and China (in the southern and western coast districts). The Chinese leprosy is a matter of some moment to other nations, for

<sup>1</sup> In consequence of the recent remarkable diminution of leprosy in Norway the well known asylum at Malta and one of those at Bergen have been closed for that disease. Dr. Hansen informs me that "the number of lepers in Norway at the end of 1904 was 222 in their homes and 257 in the asylums."

emigrants from that country have planted new foci for the extension of the disease in more than one distant place in both hemispheres.

Leprosy exists throughout the Indian Peninsula, being especially prevalent, both absolutely and relatively, in the Bardwan and Kumon districts of Bengal and the Bombay part of the Deccan. There are asylums at Calcutta, Bombay, and many other places, but it is estimated that at present not more than 2 per cent of the Indian lepers are thus cared for. It is rare in Sind, common in Ceylon and the Andaman and Laccadive Islands. It is also frequently met with in Burma, Siam, Cochinchina, and the Straits Settlements, where, at Penang, there is a large asylum. Numerous cases occur in Java, Sumatra, and the other islands of the East Indian Archipelago, and also in Borneo.

As regards Africa, we find the disease extensively diffused in Egypt, both in the Nile basin and along the shores of the Mediterranean and Red Seas. It is also prevalent in Abyssinia—on the coasts as well as in the plains and hill districts. It occurs in Algiers and Morocco, but here it has probably been more often confused with syphilis. It is found in the Canaries and Madeira, and less commonly in the Azores, and it also exists at St. Helena. On the West Coast it extends from Senegambia to Cape Lopez, according to Tonkin it is more prevalent in the inland districts far away from the coasts and rivers. It is probably endemic in the interior of Africa, for it is not unfrequently found in slaves from the Sudan and elsewhere. The disease is common in South Africa, where it is generally believed to be increasing, and a large leper settlement is in active work at Robben Island near Cape Town. Since 1850 an endemic centre has sprung up among the Zulus who had migrated to Natal. Livingstone met with it in his travels, and there is now a centre in German East Africa. On the East Coast cases are also found at Zanzibar, Mozambique, and in the islands of Madagascar, Mauritius, St. Marie, Réunion, Rodrigues, and the Seychelles.

In Australia cases of leprosy have been cropping up within the last thirty years, chiefly among the Chinese, but also to a less extent among the white colonists. From 1883 to the end of 1904, ninety six cases had been under the cognisance of the New South Wales Board of Health: at the latter date there were seventeen in the lazaretto at Little Bay near Sydney—seven being natives of New South Wales of European descent, five whites from other countries, and the rest coloured. A rigid system of segregation has been adopted in this colony. Several cases, chiefly Chinese and Kanakas, have occurred in Queensland and Victoria and one or two in other parts of Australia.

In New Zealand a small centre has long existed among the Maori of Taupo and Rotorua. The disease, which is chiefly known by the name of "Ngerengere," is believed to have been introduced towards the end of the seventeenth century; it appears to be dying away. Two cases have been reported among the whites, and one in a Chinaman.

The Hawaiians, in proportion to their numbers, are probably more afflicted with leprosy at the present time than the inhabitants of any

other part of the world. The leper settlement at Molokai was established in 1865, shortly after a manifest increase had been observed in the number of cases throughout the islands: from that date to 1895 5124 lepers were received. The average number of the leprous population in the settlement for some years has been upwards of 1000.

The disease is also well known in the Philippines, Fiji, Tahiti, and other islands of the Pacific, but information on the subject except as regards Fiji is scanty.

The western hemisphere was probably first invaded by leprosy in the seventeenth century—indeed from the time of the importation of negro slaves from Africa. It is also probable that some cases came from Portugal and Spain. In certain parts of America and in some of the West Indian Islands the disease is at the present time very common; other places, on the other hand, are quite exempt. There are five endemic centres in the northern continent—at Louisiana, Florida, California, at Tracadie in New Brunswick, and at Cape Breton. In the first-named district it appears to be increasing, while in New Brunswick it has decreased during the last few years. There are a few cases also in Texas and South Carolina.

The disease is also to be found among the Chinese in British Columbia, and among the Norwegians of Minnesota, Wisconsin, and Dakota. In none of these districts is there much evidence of its spreading. The Norwegian lepers, in fact, have diminished from 160 known cases to under 30. White estimates the "sporadic" cases to be found in other states of the Union, chiefly in the large cities, at about 20. A commission appointed in 1899 ascertained the existence of not less than 278 cases for the whole of the United States.

In Central America leprosy is generally diffused in Mexico and Costa Rica, and is occasionally seen in Nicaragua.

In South America it is especially common in British and French Guiana, less so in Dutch Guiana. Brazil is largely infected, and it also occurs in North Argentina and Paraguay. There are many cases in Ecuador, very few in Peru, and apparently none in Bolivia and Chile. It is common in Columbia and Venezuela, and in several of the West Indian Islands, for example, Jamaica, Barbados, Trinidad, Cuba, and Hayti.

**Varieties of Leprosy.**—Although leprosy is, undoubtedly, a distinct and fairly definite disease, the cases may be conveniently grouped under at least two, possibly three, categories—according to certain predominant *clinical* characters—thus we have the so-called "varieties" or "forms" of leprosy, namely, (1) the *nodular* (also called "tuberos," "tuberculated," etc.), (2) the *smooth* (also called "anæsthetic," "non tuberculated," "tropho-neurotic," etc.), and (3) the *mixed*. In the first, the skin is primarily and chiefly affected; in the second, the nerves are most implicated; and in the third, both the skin and nerves are more or less extensively diseased. These three varieties are not distinct processes, for the two first often pass into each other, most tuberos cases, indeed, at some

time or other exhibit peripheral anæsthesia, and often terminate in "mixed" leprosy; and more rarely the so-called anæsthetic form may develop "tubers" on the skin. This artificial classification, therefore, only adopted here for convenience of description. The "mixed" form is by no means universally accepted as a variety, as it is by many considered to be but the complete manifestation of the disease. "Macular leprosy, also spoken of formerly as a variety, is merely an early stage." "Leprosy mutilans" and other names have been given to cases which present particular features.

The percentage of the three forms varies much in different places as shewn in the following table:—

	Trinidad. (Rake.)	Demerara. (Hillis.)	India. (Commission.)	Norway. (Danielssen.)
Nodular . . . .	36	21	12·2	51·6
Smooth . . . .	44	62	56·6	33·3
Mixed . . . .	20	17	31	15·1

It is urged by Hillis and others that the three forms run their course each in a peculiar manner; and, as will be seen below, it is true that the clinical features in the two chief classes of cases differ throughout the progress of the disease in important particulars, the differences depending upon the order of invasion of the tissues.

**Etiology.**—It will be seen later that leprosy is always associated with a specific bacillus, and also that—with the exceptions noted, all of which need confirmation—this bacillus has not yet been certainly cultivated outside the body, or undoubtedly inoculated, with subsequent proliferation into the tissues of man and other animals.

Although it is thus evident that in the case of leprosy only the first of Koch's postulates is as yet with absolute certainty fulfilled, nevertheless from the close analogy between the bacilli of leprosy and of tuberculosis, and from other considerations, pathologists have felt justified in accepting the *Bacillus lepræ*, or the poison secreted by that organism, as the true cause of the malady. This being granted, we must regard leprosy as a "specific infective disease," and admit the possibility of its communicability from one person to another. Moreover, as the bacillus has never yet been found growing outside the human body, although it is thrown off in great quantities in leprosy discharges, we are driven to acknowledge that its only source at present definitely known is in the bodies of lepers.<sup>1</sup>

In discussing the principal etiological factors which have been ascribed to the disease, we shall see that the question is a difficult one, and that

<sup>1</sup> If the acid-fast bacillus recently found in certain diseased rats (vide p. 672) prove to be identical with the *B. lepræ*, the above statement must be modified.

The present state of our knowledge, no decided conclusions can be arrived at. We shall briefly inquire to what extent practical experience confirms the above considerations.

*Contagion.—Historical Evidence.*—It has been argued that history has proved the contagiousness of leprosy, and that in remote times it must have been spread in that way from Egypt to the Levant, Greece, Italy, the rest of Europe. The absence of early record of it in a country does not prove that the disease did not exist there; but we may assume that the diffusion of knowledge from the East would tend to the observation and recognition of such a disease. Moreover, other possible etiological factors which obtain at the present day must have been existent then, and, as we shall see, it is by no means improbable that the virus of the disease may invade the human system in more ways than one.

It has been further maintained that the contagiousness of leprosy is proved by the diminution or extinction of the disease after the segregation of lepers in the Middle Ages in England and other parts of Europe. We know, however, that the isolation of lepers was never absolute; and that although they may have had to appear in a special dress and with a ring of clappers, and were objects of abhorrence, they were frequently allowed, nevertheless, to wander about and shed their bacilli over the surface of the earth. It is needless to say that antiseptic precautions were then unknown. We may indeed conclude that historical evidence, though indicative of some amount of human transmission of the disease, does not prove its communicability only by contagion.

*Contagion at the Present Day.*—Most of the alleged instances of communication of leprosy from one person to another have occurred in countries where the disease is endemic, and are therefore open to the objection that the virus may have been acquired otherwise than by contagion. Even in such countries instances of apparent contagion, with solid data, are comparatively uncommon. For instance, during the stay of the Leprosy Commission in India, eight cases of the kind were brought forward, but only one stood the test of close examination. This case was that of a sweeper in the Calicut Asylum, in whom leprosy appeared after dressing the sores of the inmates for twenty years. At Trinidad, within ten years, only one case was noticed of apparent contagion—that of a man who developed the disease two years after living with a leprous man. Many cases, however, have been recorded in India, British Guiana, and other parts of the world; and Hillis reports 60 cases of leprosy contracted by healthy persons living in the immediate vicinity of the Bahama Asylum. Donovan has recorded a case from the Lepers' Home

Spanish Town, Jamaica. A cook after being employed there for seventeen years exhibited the disease. He frequently slept at the asylum, and was assisted in his work by two leper inmates. No member of his family had ever been affected. Supposed instances of contagion have also been brought forward within recent years by Moore and Cayley in India, Ross in South Africa, Heidenstam in Cyprus, Münch in South Russia, Simons in South Africa, Taché in New Brunswick, Hellat in the



Baltic Provinces, and Azevido Lima in Brazil; some of these reports related to attendants and others employed in leper asylums.

The accounts of Europeans who have contracted leprosy in leper countries are far more important, for such subjects are probably less dirty and careless in their habits, and cannot, like some natives, be regarded as having any special tendency to take the disease. Several instances are on record of Europeans who were associated with lepers and acquired the malady, for example, Fathers Damien and Gregory in Molokai, Father Boglioli in New Orleans, a French Sister of Mercy in French Guiana, and another in Tahiti. The two latter are said to have pricked their fingers with needles while sewing lepers' clothes. Small isolated outbreaks, traceable to the settling of lepers in districts previously free from leprosy, have also been reported in Russia, Louisiana, New Brunswick, Cape Breton, and Parcent in Spain. It must be admitted, however, that in all these cases the virus may have been introduced through food, or by other means.

On the other hand, there is a mass of negative evidence. Thus, the Dominican Nursing Sisters in the Trinidad Asylum have been in constant contact with the lepers for thirty-six years, and not one of them has become infected. The experience in a large number of other asylums has been the same. Zambaco Pacha relates the case of the resident priest at the asylum at Constantinople, whose family for three generations lived among and freely mixed with the lepers, without contracting the disease; and similar instances are indeed innumerable. As pointed out by Ashburton Thompson, the case of the Kokuas and Kamaains at Molokai is suggestive; these people, although for many years in frequent and close communication with the lepers of the settlement, have not acquired the disease in any remarkable proportion. Medical men in various parts of the world have pricked their hands in surgical and post-mortem operations on lepers and have not taken the disease. Many accounts have been published of healthy persons cohabiting with lepers for years with impunity. Three cases in point have been recently under my own observation in England. Leprosy has not yet spread from the Chinese in California, nor from the Norwegian lepers who emigrated to North America, with the exception of one case in Minnesota reported by B. Foster; and although there is always in London, Paris, and other European centres an appreciable number of patients who have contracted leprosy abroad, the disease, with the exception of the cases about to be referred to, has not been acquired by people with whom the lepers have associated.

*Instances of Transmission in Leprosy-free Countries.*—The most important case of this kind yet known in this country is that recorded by Dr. Hawtry Benson in Dublin. An Irish soldier returned from India with fully developed leprosy. For a year and a half his brother slept in the same bed with him, and he wore the leper's clothes after the latter's death. Three years later this brother, who had never been out of the United Kingdom, manifested leprosy and died of it. The diagnosis was con-



ed by medical men well acquainted with the malady, and we may  
 t the case as conclusive. Similar instances, perhaps not quite so  
 rom doubt, have been also recorded by Drs. Liveing, Rees, Atkinson,  
 others. A case apparently free from doubt is recorded (1904) by  
 of Strassburg. A man suffering from leprosy acquired in Tonkin  
 n Strassburg. In 1902, his nephew, aged nineteen, who had never  
 d out of Urbach, a leprosy-free area, presented himself at the  
 with leprosy. His uncle had lived in the house and in close  
 ation with the lad for two months.

Te must therefore, on the whole, admit that in some cases leprosy  
 een communicated from one person to another. Possibly such  
 ces would be brought before us in greater numbers were it not that  
 sease is one of very slow incubation, and its prodromes are frequently  
 and overlooked. Even with diseases of acknowledged contagiousness  
 bvious early symptoms, it is often difficult to trace the contagion.  
 f leprosy be "contagious" in the ordinary sense of the term, it must  
 in a comparatively very slight degree, far less so indeed than tuber-  
 s. We shall see how difficult it is, to say the least, to inoculate  
 isease, and we have no evidence that the bacilli can enter the body  
 gh the unbroken skin. When it spreads, therefore, as it has done  
 rtain countries to a significant extent within a few years, we are  
 ied in asking whether there must not be something more than mere  
 gion to account for its increase.

*Vaccination as an alleged Etiological Feature.*—Certain persons blindly  
 idiced against the practice of vaccination have sought to lay the  
 id of leprosy to its charge. For many years the minds of observers,  
 potent and otherwise, all over the world have been open to the possi-  
 y of the introduction of the disease with the virus of vaccinia, and it  
 emarkable how few authentic instances have been brought forward of  
 a supposed dissemination; this question is fully considered by Dr.  
 and in his article on "Vaccinia" in Vol. II. part i. (p. 735), and it is  
 wn that the alleged cases of transmission of leprosy by vaccination  
 open to serious doubt, and that, assuming the presence of leprosy  
 illi to be necessary to produce leprosy, no danger need be apprehended  
 n the vaccine lymph even of a leper, provided he be vaccinated on  
 lthy skin.

*Heredity.*—Until recently a belief in the heredity of leprosy was  
 ely spread among medical men, as it still is among the ordinary  
 abitants of infected countries; and it was often pointed out that the  
 ase seemed to prevail in certain families. In such cases, however, the  
 ction appeared in collateral members rather than in the direct line.

Even if it be true, as suggested by Virchow, that an inherited  
 osition to the disease may exist in certain families (and there is reason  
 oubt whether such a predisposition be transmitted to any large extent),  
 ose investigation of the facts indicates that heredity can have but  
 e effect in the dissemination and perpetuation of leprosy.

The following considerations bear upon this question :—

(1) In all the leprosy countries of the world a genealogical family taint can be traced in comparatively few cases; and even those in which brothers or sisters and collateral branches are or have been affected, are not so general as might be supposed. Thus, in India, the Commission could only discover family histories of the disease in 5 or 6 per cent of the lepers seen; and in Crete, Vandyke Carter found a similarly small proportion of "hereditary" cases. Among 118 patients at the Tarn Taran Asylum, 38 stated that one or more of their blood-relations were or had been lepers, but of these, in only 16 had one or both of the parents or grandparents been affected. It is, moreover, not stated whether the disease made its appearance in the latter before or after its development in their offspring.

(2) Immigrants from leprosy free countries, or their immediate descendants, in whom there could be no hereditary trace of the disease, frequently become leprosy in infected countries.

Of 42 cases of leprosy recorded by Blanc at New Orleans 12 were natives of foreign countries (7 German, 1 Austrian, 1 English, 1 Irish, 1 French, and 1 Italian), and of the remainder, 18 were the children of foreign-born parents (chiefly German and Irish). "from which we conclude," he says, "that if the disease be hereditary it must be derived from a variety of foreign sources, and, if acquired, then it seems to attack the children of immigrants as often as those of the older native families."

(3) One or more of the younger generation often become lepers, while the parents and grandparents are not affected, and these latter occasionally become diseased some time after the children.

(4) When lepers beget children the latter frequently remain free from the disease; for instance, in the Almona Orphanage, where they are separated from their mothers at an early age, only one out of fifteen has manifested leprosy; in the Trinidad Orphanage, however, one in eight became affected.

Blatt, on the other hand, reports two cases in Mexico in which the subjects were removed at birth from leprosy mothers, brought up in districts free from leprosy, amid healthy surroundings, and never in contact with lepers, but who nevertheless became diseased at or after twenty years of age. He regards these as good instances of hereditary transmission.

Perhaps the strongest evidence yet adduced against the heredity of leprosy is that brought forward by Hansen, who made a special journey to North America to discover what had become of the 160 known Norwegian lepers who had emigrated and established themselves in the States of Wisconsin, Minnesota, and Dakota. He found that not one of their descendants, as far as the great grandchildren, had exhibited disease.

(5) Lepers are extremely sterile, hence, even if they were allowed to marry freely, the disease, if its transmission depended on heredity, would soon become extinct. At Molokai, in eighteen years, of 2

lepers who were incarcerated, but with free intercourse among themselves, not more than 26 children born in the settlement were found living at the end of the period, and of these only two had become lepers.

In India it has been calculated that the average number of children to each marriage between lepers, or between a leper and a healthy person, is less than one. At Tain Taran 21 children were the progeny of 55 marriages. Only four females in that asylum in whom the disease had already declared itself gave birth to children, and these amounted to five.

Two lepers, a male and female, each married, under my care in England have had children since their disease appeared—the man four, and the woman two. In both families the children have remained perfectly healthy, as well as the wife of the one and the husband of the other.

(6) Cases of congenital leprosy are very rare, of the few instances recorded in which infants were born with supposed marks of the disease upon them, it is quite possible that the symptoms were really those of syphilis. Navairo has reported two cases in Colombia as occurring in 1847 and 1848, and two infants at Trondhjem are reported to have been leprosy at or shortly after birth. Although children are sometimes affected, the enormous majority of the cases shew the typical period of onset of the disease to be in young adult life; some few lepers, however, do not present the first signs of leprosy until extreme old age. I myself saw in Norway three patients upwards of eighty years of age, who had been leprosy for two or three years only.

*Influence of Diet.*—At various times and in various countries a great many articles of food have been declared to be the cause of leprosy, but although it is quite possible that the bacilli may sometimes gain entrance to the body with the ingesta, and that the tissues of those who partake of certain foods may be rendered less resistant or more susceptible to the growth of the micro-organism, we cannot, on the facts before us, definitely connect the disease with any particular diet.

A causal relation has been alleged between leprosy and a vegetable or non-nitrogenous diet, a diet of salted food, of food without salt (ably argued by Munro), of pork, of fish, and of many other things, and the use of contaminated water has been suggested by Dr. Laveing and others.

The fish hypothesis, which dates back from the time of Avicenna, has been supported by various writers, and in recent years particularly and most ably by Mr Jonathan Hutchinson. It is argued that the chief centres of leprosy are on the sea coasts, or along the borders of large rivers, where the people live chiefly on fish—often more or less decomposed, uncooked, dried or salted; but it is likewise true that the disease is also largely prevalent in places far from seas and rivers, and where fish cannot be obtained, for example, in the mountains of Kurdistan, many parts of India, Kashmir, and so forth. In India certain castes of Jains, Brahmins, and Banias religiously abstain from all animal food, and many of them at least never taste fish—nevertheless leprosy occurs amongst them. In the hill districts of Almora and Dehra Dun the

Commissioners met with lepers who not only had never eaten fish, but who did not even recognise the form of a fish when shewn to them. Fish and preparations of fish of all kinds have been carefully examined for bacilli in leprous countries, but without success.

Mr. Hutchinson has lately visited South Africa and India, especially to investigate the evidence in connexion with the fish hypothesis, viz.: that the use of unsound fish as food is the main cause of leprosy—and he believes that the facts which he has collected are practically conclusive. He doubts the statements of natives who do not admit ever having eaten fish, and he points out that even in mountainous and inland districts dried preparations of fish are frequently to be met with. This authority, however, met with instances in Africa where “children who had been bred up in company with a leper, but who were descended from healthy parents, and who had never eaten fish, had become the subjects of the disease.” He believes that this “commensal” communicability is, nevertheless, very rare.

*The Influence of Poverty, etc.*—That poverty and bad hygiene have an indirect effect on the prevalence of leprosy must, however, be freely admitted. The poor in all the countries in which the disease is endemic suffer more frequently than the rich, although the latter by no means escape; and we may well believe that insufficient or innutritious diet may render people more prone to its acquisition. It is thought by many, indeed, that the diminution and extinction of leprosy in most of the countries of Europe was due more to the improved well-being of the people as to food, clothing, cleanliness, etc., than to the measures of isolation.

*The Influences of Race, Climate, etc.*, need only be alluded to very briefly. No nations are exempt, and the disease may occur in the coldest as well as in the hottest climates, in moist or in dry districts, in plains or on mountains. Nor has any direct connexion been shewn between leprosy and other diseases such as syphilis, tuberculosis, scabies. With leprosy, as with other diseases, anything which lowers vitality may render the system more liable to its acquisition and less able to resist its progress; and it is also possible that any breach of the skin may facilitate the introduction of the virus. In this latter way, possibly the bites of insects, scabies, and other affections of the kind may have an indirect influence, although this has not been proved.

We know by definite experimental proof and by clinical observation that tuberculosis—the first cousin of the disease under consideration—may be introduced into the body by more than one channel, through the respiratory and alimentary passages as well as through the skin, and we may reasonably suppose that leprosy likewise may be acquired in as many ways, although the paths of entry have not as yet been fully traced.

*Pathology.—Anatomical Changes.*—Post-mortem examination, or the observation of excised parts during life, invariably shews that the ultimate phenomena of leprosy are due to the development of a characteristic

leptous neoplasm in certain tissues of the body. This new growth is largely composed of so-called "lepra-cells," many of which are agglomerations of bacilli, the others being true cells probably produced by proliferation of the tissue elements. These latter cells as well as the accompanying leucocytes may also contain bacilli.

The state of some of the more important organs commonly affected may be described, and a full description given of the neoplasm as observed in the skin.

*The Skin.* A young or growing nodule of the skin when cut into shews the epidermis normal, but the corium rather firmer than in health; a little viscid fluid can be squeezed out. In the older growths the cut surface is granular, and of a yellowish-white colour, and the substance is softer. The subcutaneous tissue is also sometimes infiltrated, and has a gelatinous appearance, but, instead of softening with age, it becomes firmer. Occasionally a diffuse infiltration is developed only in the subcutaneous tissue. The walls of the vessels are thickened by the infiltration of the lardaceous looking material, and the nerves are also increased in size by the same deposit, and by the existence of a definite neuritis.

The sweat-glands, the sebaceous glands, and the hairs are gradually compressed by the surrounding leprous infiltration, and finally they quite disappear. In some cases hypertrophy of the arrectores pilorum seems at some time to take place, and at first there may be also hypertrophy of the sebaceous glands and an increased secretion of sebum. As the growth increases towards the surface the epidermis is pressed upon and becomes attenuated. The deeper parts of the subcutaneous tissue and the subjacent tissues are at first not directly involved.

Under the microscope, a vertical section of a cutaneous nodule exhibits, in place of the normal connective tissue, which has become altered or destroyed, a large collection, or several clusters, of characteristic lepra-deposit, forming a mass which is situated more often in the middle or deeper layers, but sometimes also in the upper and papillary layers of the corium. In the older growths, which extend almost to the surface, the papillary body becomes thinned with obliteration of the papillae and thinning of the rete mucosum, but in early nodules the latter with its interpapillary processes may be intact, and a band of unbroken connective tissue may be seen between it and the affected part of the corium.

The masses of bacilli and cells, thus constituting the nodule, are at first principally grouped around the vessels, nerves, and glands, and they can be seen to extend along the course of the lymph-channels. In a subcutaneous nodule from a prepucium examined by myself, the new growth was largely made up of the immensely thickened blood vessels, which, as they entered the nodule, shewed a dense infiltration of the adventitia, media, and intima, with obliteration of the lumen.

Most of the so-called "lepra-cells" are very similar in superficial appearance, i.e. when unstained by bacteriological methods, to the



granulation-cells of lupus, syphilis, etc. They vary in size from that of an ordinary leucocyte to four times that size or more, and, when stained with hæmatoxylin or by ordinary histological methods, many of them exhibit one or sometimes two nuclei. As will be seen directly, they can be shewn to contain specific bacilli in greater or less numbers, or to be made up of more or less dense collections of bacilli.

Occasionally very large multinucleated cells, somewhat resembling the "giant-cells" of lupus, are seen in the peripheral or deeper parts of the growth, and these may have arisen in several ways, for example by the continued growth of one cell and subsequent proliferation of its nucleus, or by the swelling and coalescence into one mass of the endothelial lining of a small vessel or capillary. The larger ones are often vacuolated. Hansen and Thin believe that when true "giant-cells" are seen, the growth is tuberculous and not leprorous. Thomas, Benoit, and Boinet, and others, have also described large multinuclear cells as sometimes present in the leprorous neoplasm. Bergengrün's and Dolin's observations place the matter beyond doubt, viz. that they do exist in leprosy; these observers shew that they are formed by the rapid multiplication of the lymphatic endothelial cells and their fusion into a plasmodium, as suggested above.

Besides undergoing fibrous transformation within their substance the developed nodules may exhibit desquamation, vesicles, or pustules on their surface, or they may ulcerate and become covered with crusts. The sections shew that during desquamation the stratum granulosum and the elastic granules have diminished or disappeared, but that there is little change in the greater part of the cells of the stratum corneum. Vesicles and pustules, on the other hand, are produced by a raising of the whole epidermis or by cleavage of its layers. When ulceration has set in there is rapid destruction of the nodule, and cells and debris are thrown off in great quantity.

Sections taken by me from one of the erythematous macules in an early stage of the disease, in a boy at the Westminster Hospital, shewed an infiltration of the corium with an irregular cell-growth, in which some large multinucleated cells were also scattered. In this case no bacilli were then observed, although they were found in abundance in subsequently developed nodules.

The microscopical examination of a portion of skin excised from anæsthetic patch of a case of smooth leprosy of two and a half years standing shewed principally a generalised fibroid transformation of corium with more or less obliteration of glands, ducts, hair follicles, nerves, and vessels. In sections from a more recent case this change was less complete, and there was a more extensive infiltration, especially near the vessels, of an irregular cell-growth; no bacilli were seen. I have given more detailed accounts in Hillis's book.

*Mucous Membranes*.—The neoplastic lesions of the mucous membranes of the mouth and throat are very similar to those of the skin; the nodules are softer in consistence, and usually of a pale red



rid colour, or sometimes dull gray and opaline. They ulcerate more readily.

There are two chief varieties of the leprous *tongue*. In the first, the *dorsum* may be covered with discrete nodules, varying in size and quickly ulcerating, and separated by furrows. Under the microscope a new growth is made up chiefly of embryonic cells, with comparatively few typical lepra-cells, and their vascularity is slight; in many parts they shew fibrous transformation. The growth may be seen extending through the mucosa and submucosa to the muscles, the fibres of which are separated and destroyed. In the second, the *dorsum* is occupied by a diffuse leprous infiltration, and divided into raised areas by longitudinal and transverse grooves; the epithelium often becomes detached in grayish flakes. The neoplasm in these cases is almost entirely composed of the lepra-cells, and there is no tendency to fibrous transformation. As the result of ulceration and cicatrization of the growth in the *mouth*, the mouth may become extremely stenosed and incapable of being opened.

The leprous infiltrations of the pharynx, larynx, and other mucous membranes exhibit very similar microscopical characters. The edge of the *epiglottis* is often affected very early, becoming thickened and nodulated; and ultimately many of the ligaments, muscles, and cartilages of the larynx may become infiltrated with new growth, leading to ulceration and cicatricial contraction. In this way, as well as by occlusion from projecting nodules, the glottis may become completely stenosed.

*Nerves*.—The nerve-trunks most frequently invaded by the leprous growth are the median and ulnar in the upper extremity, and the posterior tibial and peroneal in the lower. The facial and the radial are less commonly invaded. According to Danielssen the cutaneous palmar nerve is the first affected; but, indeed, any nerve may be attacked sooner or later. Leloir describes three cases in which the recurrent laryngeal was affected, and he thinks that in this way the aphonia sometimes present may sometimes be produced. It can be shewn that the discoloured and anæsthetic patches of skin are in direct relation to the deposit in nerves supplying the parts, and their irregular distribution is explained by the fact that only certain groups of fibres may be implicated. To the naked eye the diseased nerve shews along its course fusiform, reddish-gray swellings, often marked with yellowish streaks of fatty degeneration; and the deposit may have a translucent or gelatinous appearance. These thickened segments may be twice or four times the diameter of the rest of the nerve-trunk, and they are often larger where the nerve is more superficial, for example behind the internal condyle of the humerus, or below the head of the fibula, in which positions they can frequently be felt by the observer's finger.

Microscopically the leprous neuritis is similar to that mentioned in connexion with the nerves passing through a cutaneous nodule. The swellings are chiefly due to the presence of numerous lepra-cells, which infiltrate the perineurium and produce a perineuritis: they are also to be

seen situated in the endoneurium, and between the individual nerve fibres, giving rise to neuritis and degeneration. Hyaline thickening of the neurilemma may ensue, the axis cylinders become disintegrated and the whole fibre altered. In old-standing cases, in which the action of the disease has been arrested, the nerve-trunk may be atrophied, and represented only by a cord of fibrous tissue.

*Lymphatic Glands.*—The lymphatic glands are sometimes invaded and may then be enormously enlarged, the neoplasm reaching through the lymphatic vessels coming from the parts affected—especially in the nodular cases. Those most frequently engaged are the tonsils, glands from arrest of leprous material from nodules or ulcers in the lower extremity, and the cervical from disease in the larynx, etc. The axillary, bronchial, mesenteric, lumbar, and other glands may also be affected. It must not be forgotten, however, that these glands, especially those connected with viscera, are also frequently enlarged from causes of tuberculosis. Under the microscope the adenoid tissue is seen to be more or less replaced by lepra-cells, and in old cases there is sclerosis, with thick bundles of connective tissue. Caseation, moreover, may take place,<sup>1</sup> and occasionally the whole gland may suppurate.

*The testes* are often the seat of leprous deposit, although in some cases there may be no naked-eye appearance of its presence. The gland is sometimes, however, tough and hard to cut. The microscope shows an increase of connective tissue, with the characteristic cells among the fibres.

*The liver* may not show any naked eye change, the leprous growth, which is sometimes present, occurs as a diffuse infiltration, principally in the interlobular connective tissue, and causes a mild form of interstitial hepatitis.

*The spleen* shews no naked-eye changes, but bacilli-bearing cells may be found in profusion.

The remaining abdominal organs likewise shew no well marked alterations to the naked eye.

*The Spinal Cord.*—Danielssen and Boeck described sclerosis and meningitis of the cord; Tschirnow found changes in the posterior cornua.

The gray matter opaque and granular, the vessels lessened in number and a cellular infiltration of the lymphatic sheaths. Spinal lesions have also been alluded to by other pathologists (e.g. Voit). On the other hand, many observers, including Hansen, Neisser, and Rake, have failed to find anything definite in the spinal cord. The ataxia sometimes present in advanced cases may be due to lesions in the posterior column independently of leprosy.

After this account of the grosser specific changes in the various organs, brief mention may be made of certain affections, whose precise relation to leprosy is not as yet clearly understood.

Hansen maintains that caseation never occurs in the leprous tissue, and that its presence indicates tuberculosis.

*tuberculosis* is extremely common in lepers. In the last 109 autopsies Trinidad Asylum tubercle of one or more serous membranes was in 33 instances, or in 30 per cent. Guinea-pigs inoculated with material from the autopsies readily manifested tuberculosis. As the deaths from the latter disease at the Trinidad General Hospital during the same period were only 18½ per cent, we may assume that lepers are more liable to tuberculosis than other people.

*Renal disease* is even more frequent. In the same 109 autopsies 35 cases, or 32 per cent, shewed some form of nephritis; while in the Trinidad General Hospital only 7½ per cent of the deaths were due to nephritis. In none of the kidneys of the above-mentioned 35 cases was there any evidence of leprosy. The disease was probably due to septic absorption and toxæmia, and possibly also to the increased strain thrown on the kidneys by the destruction of the sweat-glands so common in leprosy.

Absorption from leprosy ulcers or abscesses sometimes produces infarcts in the viscera, and sometimes lardaceous changes occur, especially in the liver and spleen.

Willis and Arning have described specific ulceration of the large intestine in leprosy; but in Trinidad, when such ulcers were present, they appeared to be associated with kidney disease, or due to causes unrelated with leprosy.

**Bacteriology.**—That leprosy is due to the presence in the system of a specific micro-organism is now admitted by all pathologists. Its discovery was made by Armauer Hansen in 1871, although a suspicion of the existence of something of the kind seems to have been in the minds of other observers before that date. Both Virchow and Wyke Carter had called attention to the presence of granular matter in the typical lepra-cells, and Sir P. Manson had actually attempted the isolation of the "germ," which he believed to exist in the cells and around the nodules; but the Norwegian investigator was the first to recognise in the granules the microbe which he named the *Bacillus*

In 1874 Hansen published, in Norwegian, an account of his discovery, and, in 1880, a still fuller report in German, with drawings of the bacilli. In the same year Neisser, working at the San Lazaro Hospital, Vienna, and employing the new aniline dyes, placed Hansen's discovery beyond doubt; within the next few years the bacilli were found in leprosy material from all parts of the world. It may now be affirmed that the bacillus is existent in the body of every leper at some period, at some stage of the disease, and that it never occurs in the bodies of those who are not lepers.

**Morphology.**—The organism is a rod-like, vegetable parasite, belonging to the Schizomycetes or fission-fungi. Its length is half to three-quarters the diameter of a human red blood-corpuscle, and its breadth is one-fifth of its length. Each rod has an outer mucilaginous envelope, the innermost layer of which retains the aniline dye, and thus the internal structure of the bacillus may be obscured. There can, how-

ever, be made out with very high powers, within the substance of the bacillus (1) Highly refracting oval spores, (2) ordinary protoplasm, and (3) granules. With certain reagents, such as iodine, strong sulphuric acid, borax methyl-blue, hæmatoxylin, and osmic acid, these granules stain deeply, the protoplasm remaining unstained. A beaded appearance may thus be produced. Hansen considers that the "spores" and "granules" are merely evidences of the disintegration of the bacillus. Although spores have been discovered within the bacillus they have not yet been seen free. The parasite multiplies by transverse fission, and is non-motile.

The bacilli of leprosy and of tuberculosis resemble one another in certain respects, especially in their staining properties. When stained with a solution of fuchsin, or some other aniline dyes, in water containing aniline oil (or 5 per cent of carbolic acid), they can both be exposed to the action of certain mineral acids for a short time without being decolourised, or are "acid-fast", thus differing from most other bacilli which when brought into contact with the acid immediately lose their stain. However, a simple watery solution of fuchsin (without any mordant) is used, the leprosy bacilli alone will retain the stain after immersion in dilute nitric acid. Other points of difference are as follows:

(1) Leprosy bacilli are generally present in sections in immense numbers or in masses, and are not sparsely scattered as are those of tuberculosis. (2) they occur principally in dense collections in the lymph spaces, are not usually solitary or in small groups as in tuberculosis, and not typically in giant cells when these are present; (3) they are invariably rather smaller.

Although they can be shewn by treating fresh tissue with solution of potash, and by various aniline dye methods, they are well demonstrated in the following manner:—

(1) The juice expressed from a nodule, or the discharge from a leprosy ulcer, is smeared over a thin cover-glass, dried and fixed as a thin film by passing through a smokeless flame, or a thin section of a leprosy growth may be spread out on the cover glass. (2) the latter, with the dried material upon it, is immersed or floated face downwards for about twelve minutes (sections may require a longer time) in warmed Ziehl's solution, prepared by adding to distilled water 100 c.c., carbolic acid 5 grammes, alcohol 10 c.c., and fuchsin 1 gramme.<sup>1</sup> (3) the preparation is then decolourised by placing it for a few minutes in 25 per cent nitric acid; (4) subsequently it is passed through 60 per cent alcohol, and (5) finally well washed in distilled water.

The cover glass may now be examined at once in water; or better it may be dried, cleared, and mounted in xylol balsam. Sections should be dehydrated by soaking in absolute alcohol, then passed through bergamot or clove oil and mounted in xylol balsam. In all cases a ground, or contrast stain of methylene blue or iodine green may be superimposed by steeping the preparation in a dilute aqueous solution of the dye, after the

<sup>1</sup> Ehrlich's solution is also efficacious.

acid has been washed out; or Gabbett's acid blue solution may be used in place of the nitric acid and separate ground-stain.

Thus prepared, the leprosy bacilli are seen as bright red beaded rods; the elements of the tissue having lost the red colour through the action of the acid. It has been found that bacilli which have been in alcohol take the stain better than those which are treated directly.

Leprosy bacilli are very resistant. Kobner found them in a fragment of tissue which he had left forgotten in a piece of paper for ten years. In Trinidad they were found in the remains of a nodule which had been inserted beneath the skin of a fowl two years before. The bacilli still took the characteristic stain, though the nodule was reduced to caseous detritus. Lelour had a similar experience with nodules which had remained two years and a half in the peritoneal cavities of guinea pigs. He also dried a piece for twelve days in a stove, and on making sections found numerous bacilli which took Ehrlich's stain. As has been truly remarked by Arning, we cannot at present say with certainty, by our histological methods, whether leprosy bacilli under examination be alive or dead.

By a special mode of preparation of the tissue, Unna came to the conclusion that the bacilli of leprosy are never contained in cells; but Rake and myself, and other observers (Thin, Hansen), are satisfied that encircled cells containing bacilli can easily be demonstrated by double staining in the nodule, as well as in a scraping from a leprosy ulcer.

It may now be stated that the bacilli, in addition to lying within cells, also largely exist free in the intercellular substance and among the elements of the tissue. In whatever way the specimens are prepared, as sections or as cover-glass films, a number of cells may be injured or broken up by the process, and their contained bacilli set free. Moreover, a lepra cell may disintegrate in the course of nature, and leave a group of bacilli in its place. It is also probable that the secretions from the bacilli have a directly poisonous effect on the tissue elements in the neighbourhood, and, setting up inflammation, cause an accumulation of leucocytes. The latter may then, like phagocytes, take up bacilli, become enlarged, ultimately suffer disintegration of the nucleus and alteration of the cell substance, and finally be represented by detritus and bacilli which have perhaps meanwhile multiplied. None of these considerations, however, are sufficient to explain the appearances so fully demonstrated by Unna, Bergengrün, and Gerich and Herman, who have proved that the majority of the bacilli of a leprosy nodule occur in cylindrical and irregularly branching masses chiefly occupying the lymph and vascular channels. Herman has also shewn that in young or recent nodules similar masses of bacilli exist which do not retain the red stain after immersion in weak acid, but are easily subsequently coloured with methylene blue. If, as he supposes, it is only the older fuchsin stained bacilli that are resistant to the acid treatment, we may have some explanation of the general failure to recognise leprosy bacilli in the attempted cultivations, as will be shewn further on.



In nodules and in affected organs, brown masses or "globi" (Nisser) are often seen. These are dense collections of bacilli, more or less broken up into granules, and are probably thrombi formed in the lymphatics.

*Distribution within the Body.*—The leprosy bacillus is by no means evenly distributed throughout the body. It may be found in any vessel or tissue, or even in all (Cornil and Babes), but far more common in some than in others. In the trophoneurotic cases it is exceedingly rare except in certain nerves. Hansen and Kohner have described them as occurring in the blood, and Leloir found them in that fluid in one case out of five examined. In no case in Trinidad have they been found in the blood, although observations were made during the acute outbreak, and this has hitherto been the experience of most other observers with blood drawn uncontaminated by leprosy skin or bacilli-bearing tissue. Hansen figures them in leucocytes within blood vessels and in the endothelium of the latter, more recently they have been found in the blood by Horder, Shoemaker, Boston, and others. They have been found in the fluid of blisters raised over cutaneous nodules, but not in blisters over anæsthetic patches. The juice expressed from a tubercle nodule contains them in abundance, as does the purulent discharge from the ulcerated nodules. In a few cases only have they been seen in the discharge from ulcers of anæsthetic lepers.

When there is leprosy ulceration of the mouth, nose, or pharynx the bacilli are found in the patient's saliva. They have also been seen by Babes and Kahndero in vaginal mucus, but the Indian Leprosy Commission, who made a few observations on the point, were not successful in finding them.

The sputum of cases in which the larynx is affected may contain them in considerable quantity. In one instance they were found by the Commission in the faeces of a leper in whose saliva they had previously been demonstrated.

They have been seen by Calabrese in urine; but they have not been reported in menstrual discharge.

The tissue in which the bacilli are found in the greatest profusion is undoubtedly the corium of the skin. When the leprosy growth is well developed, sections stained for bacilli may shew masses of the latter so closely approximated that but little else can be seen in the field.

The bacilli have been found in the rete mucosum between the cells of the papillæ and other layers, and they have also been demonstrated in the hair follicles. They have not been demonstrated by Dr. Kakegawa myself in the cutaneous anæsthetic patches of the trophoneurotic cases, nor has either of us seen them in the macula or erythematous patches of early leprosy, except in one instance by myself. Hansen and others, however, appear to have found them with ease, especially in the red spots. In the nerves of the anæsthetic cases as well as of advanced cases of dermal leprosy—wherever the nerve enlargements exist—the bacilli are found throughout the neoplasm, within the cells in the sheath between the nerve fibres, and also apparently free. They are said to be



numerous in the nerves of the purely trophoneurotic cases than in those of the "mixed" cases. In very old or arrested cases of the former, in which the nerve-trunk has become atrophied, the fibres degenerated, the leprosy cells disintegrated, the bacilli may be very few or altogether absent.

They are often found in the femoral lymphatic glands, especially in the standing nodular or "mixed" cases.

The distribution of leprosy bacilli in other organs of the body and in the viscera seems to follow no general law. In the Trinidad autopsies mentioned above, the liver, spleen, and testes were most commonly invaded. In the liver the bacilli are found in the new connective tissue between the lobules, as well as in the lobule itself, among the hepatic cells; and have also been described in the substance of the hepatic cells, in the lymphatic spaces, and in the small branches of the portal vein. In the spleen they are seen in the splenic cells as well as between them, and in the testis the bacilli are found principally in the increased connective-tissue around the tubules, and occasionally within the tubuli seminiferi themselves, and in the epididymis. The bacilli are much less commonly found in the kidney—of 77 kidneys examined at Trinidad, they were present in 7 only—in the glomeruli, and in the endothelium of the renal vessels.

Among other organs in which they have been found are the ovary (Arning), the intestinal wall, the mesenteric and lumbar glands, in bone-marrow and Haversian canals (Delépine and Slater), and in striped muscle-perimysium, endomysium, and fibre. Chassiotis has described leprosy bacilli in the brain, but they were never seen at Trinidad either in the brain or spinal cord, although frequently sought; in one case they existed in the superior cervical ganglion of the sympathetic.

In the lungs undoubted leprosy bacilli are probably rare. Bonome and Arning have described them, but they were never seen in the Trinidad autopsies. On the other hand, as we have seen, pulmonary phthisis is common among lepers, and in such cases the bacilli of tuberculosis are abundant in the pulmonary tubercles and in the sputum. Damaschino has found the bacilli of both leprosy and tuberculosis in the lungs of a leper, as I too have done in one case. I have demonstrated leprosy bacilli in abundance in the trachea of another patient who died with extreme leprosy stenosis of the glottis.

*Distribution outside the Body.*—Very little is known concerning the distribution of the leprosy bacilli outside the human body. Kaurin, after numerous experiments, failed to find the bacillus in the earth, or in the dust and air of the rooms inhabited by lepers. In Trinidad, examination of the soil of graves of lepers did not shew any bacilli; and observations made on salt fish, salt pork, etc., in the asylum were negative. At the Morla Asylum the Leprosy Commissioners prepared 100 cover-glasses from earth taken from the banks and paths on which the lepers were in the habit of sitting and walking. In 7 of the cover-glasses only 9 bacilli were found, to the number of 10 altogether. At the Tarn Taran

Asylum 450 similar specimens were prepared, but no bacilli were found. Water from tanks at Bombay and Tarn Taran in which lepers bathe also gave negative results, although they could be easily detected in tanks of water in which leprosy ulcers had been washed. A large number of examinations of fish, dried and fresh, in Burma, Bombay, and Darjeeling, also failed to shew the bacilli. Flies and mosquitoes were allowed to feed on discharges from ulcers and on lepers' blood, and were afterwards examined for bacilli, but with no positive result.

*Cultivation Experiments.* Since its discovery numberless attempts have been made by pathologists to cultivate the bacillus outside the body, and up to the present time without undoubted, absolutely certain, and well-confirmed success.

Hansen kept leprosy blood in a moist chamber, and obtained a mycelial growth, which, as he afterwards admitted, had nothing to do with the leprosy bacillus. Neisser inoculated blood serum with fragments of leprosy tissue, and kept pus and juice from nodules in sealed capillary tubes. From these experiments he described three different bacilli, which, however, he failed to cultivate in generations. Arning in Hawaii, allowed pieces of leprosy tissue to macerate in water, and observed a multiplication of the bacilli, as also in the tissues of a deceased leper who had been buried for three months.

These observations were repeated at Trinidad without positive result, and numerous experiments were made with various media, including blood serum, ascitic and hydrocele fluid from lepers, and combinations of them with agar, glycerin jelly, etc. Growths of micrococci were frequently obtained, but never leprosy bacilli. In 1887 Bordin Uffreduzzi announced that he had been successful. He had passed portions of bone marrow, in which he had found free bacilli in peptone-glycerin serum, and obtained cultures of a small bacillus, often bipolar at the ends and resembling those found in the tissues, but retaining the fuchsin stain with more difficulty. Inoculations of animals with the cultivated bacilli were negative. Giantusco subsequently obtained a cultivation which Bordin Uffreduzzi considered identical with his own, and Campana has more recently described a third bacillus cultivated from leprosy material. A careful examination of specimens from all these cultures is not convincing.

Culture experiments were carried out in India by the members of the Leprosy Commission, who also thought at first that they had been successful. In one series of observations sterilised capillary tubes containing blister fluid from healthy skin were inoculated with fluid from blisters over leprosy nodules. The tubes were carried about in the axilla of one of the observers for a month, and bacilli somewhat resembling those of leprosy were then found in them. Subcultures in glycerin bouillon gave a growth of bacilli, which retained a pink stain after treatment with Ziehl's solution and dilute nitric acid, but the bacilli were shorter and thicker than those obtained from the leprosy tissues. Further subcultures resisted the action of the acid still less. Inoculations in animals

re without effect. I have myself employed a medium containing broth de from the tissues of a leper with peptone, glycerin, and agar. A with seemed to take place at first, but afterwards disappeared, and empts at subcultures proved futile. Scholz and Klingmüller have also ed in numerous attempts. Babes, E. Levy, Czaplewsky, Spronck, drowski, and several others have reported the cultivation of a "diph-roid bacillus" from cases of leprosy, differing from Hansen's in staining ctions, but which is specifically agglutinated by the serum of leprous od. Spronck's grew well in fish bouillon. Van Houtum believes that succeeded in Ceylon in cultivating a bacillus which is the true morbid ent of leprosy, although it differs from Hansen's bacillus in its staining actions and in size. Carrasquilla and Rost have published supposed ccessful results. Rost states that the smallest trace of common salt the medium prevents the growth. His experiments were repeated, ut have not been confirmed in India or by Tidswell in New South Vales. E. Weil reports partial success by means of agar medium contain- ng yolk of egg. The remarkable difficulty so far of cultivating the acillus of leprosy contrasts strongly with the ease with which the bacillus of tuberculosis can be grown outside the body, and forms indeed an im- portant distinction from it.

*Inoculation of Animals.*—An enormous number of attempts have been made to get the leprosy bacillus to grow in the bodies of animals, but in very few instances has there been any spread or multiplication of the organisms beyond the immediate neighbourhood of the inoculation. Neisser inserted a piece of leprous tissue beneath the skin of a dog, and subsequently found a growth of bacilli at the site of the inoculation. Damsch and Vossius introduced portions of a nodule into the anterior chamber of rabbits' eyes, and described infiltration of the iris, ciliary body, and Descemet's membrane with cells containing leprosy bacilli, but similar results have been obtained by Wesener, Leloir, and Campana, by implanting leprous material which had been for years kept in alcohol. Campana inoculated the vascular combs and wattles of fowls, and often obtained a local inflammatory swelling containing large cells which had taken up the bacilli in the manner of phagocytes. Köbner and Hansen led to infect monkeys, and Hilliaret and Gauche a pig. Vidal also culated a pig, and a year afterwards he found bacilli in the remains of implanted mass, but none in the surrounding tissues.

Arning, Kaurin, Leloir, and Thin have hitherto been unable to elish leprosy in animals, and the Trinidad experience has been the . During a period of ten years attempts were made with guinea- rabbits, cats, pigs, bats, fowls, small birds, a dog, and a parrot. and fowls were also fed at the asylum for long periods—some as us two years—with cutaneous nodules and pieces of viscera from but no results were obtained.

the other hand, Melcher and Ortmann, four months after inserting of a fresh nodule in the eyes of rabbits, found the cæcum, spleen, and lymphatic glands infiltrated with growths containing bacilli,

which were regarded as those of leprosy. This opinion was confirmed by Arning and Ruffer, but Wesener, who repeated the experiments, came to the conclusion that no proliferation of the bacilli had occurred, but merely a diffusion of those introduced. He and Hüppe believe that Melcher and Ortmann, like many others, have sown leprosy and reaped tuberculosis. Tedeschi inoculated a monkey in the spinal dura mater. Death occurred in eight days, and bacilli resembling those of leprosy were found in the new tissue at the site of the inoculation, and in the cerebrospinal fluid and spleen. In this case, too, it is probable that a diffusion, without proliferation, of the bacilli had taken place. Nicolle reported in 1905 the successful inoculation of a Macaque monkey with leprosy. The evidence given above, though to some extent conflicting may on the whole be regarded as supporting the view expressed by Besnier—that leprosy is strictly a human disease which cannot be transmitted to animals.

Allusion must here be made to the important discovery by Dr. Dean in 1903, and in the same year, independently, by Stephansky at Odessa, of a leprosy-like disease in rats, characterised by neoplasms in the skin glands, etc. These largely consist of enormous numbers of bacilli-bearing cells, the bacilli resembling those of leprosy in their morphological characters, their distribution, their acid-fast staining reactions, and their difficulty of culture. A “diphtheroid bacillus,” however, has been cultivated from the growths in two cases, which has the remarkable property of being agglutinated by human leprous serum. The same affection has been described by Rubinowitsch in rats in Berlin (1903), and by Tidswell in a rat in New South Wales.

*Inoculation in the Human Subject.*—A considerable number of persons have from time to time allowed themselves to be inoculated with leprous material in order to test whether the disease could be so communicated, but as yet with no positive results. Danielssen, Bargilli, Holst, and Tilsch made such attempts, but always with a negative result. Profeta inoculated himself and nine other people, and sixteen years afterwards there had been no evidence of the disease in any of them. Hansen introduced material from nodular cases into anæsthetic cases, but with no development of nodules in the latter, and similar experiments were made at Trinidad with thirty-three anæsthetic lepers—nodulation appeared only in one of them four years after the inoculation. We have, however, already seen that after some years dermal nodules may spontaneously appear in such cases. On the other hand, Arning inoculated an apparently healthy convict at Honolulu, and three years later the man manifested leprosy. This case has been regarded as conclusive, but it has since been found that several members of his family—a son, nephew, and maternal cousin—had also become lepers in the ordinary way. Indeed, for an experiment of the kind to be absolutely conclusive, it should be made in a country where leprosy is not endemic, and on a subject who could never have been in contact with the disease.

It cannot, therefore, be admitted that the intentional inoculation

**The Incubation of Leprosy.**—Many instances are on record which show that the virus may remain latent in the body for many years without giving rise to any of the symptoms of the disease. In the present state of our knowledge it is impossible to speak of any definite period of incubation in connexion with leprosy. We do not know whether its entrance is marked by any initial lesion; for although in a few exceptional cases some slight traumatic injury, with subsequent local inflammation and difficulty of healing, was observed at a variable interval before the disease was suspected, yet most of the patients are unable to point to any circumstances of the kind, or to give any notion of the date of inoculation.

Instances have been given of the appearance of the disease only a few weeks or months after the patient has come from an unaffected to an affected district; and there are others in which the pathognomonic signs have not been observed until forty years after the individual has been in a leprous country, or could possibly have been in contact with lepers. There has been a case in London of such retarded incubation, shewn by me at the Epidemiological Society in 1889, and another Englishman, lately under my care, shewed no mark of the disease for eleven years after coming back from India, whither he had been taken as a child. Since his return to this country he has been living in a small country town, and had no dealings with the East, or with any one or anything therefrom. A third instance, a young lady also under my care, shewed no sign of disease until seven years after returning home from Ceylon.

**Symptomatology.** *Nodular Leprosy*.—"Tuberculated," "tubercular," "nodular-dermal," "dermal," "cutaneous," "hypertrophic" leprosy. *Lepa tuberosa*, L. *tuberculata*, L. *tuberculosa*, L. *dermoplastica*, *Lèpre systématisée tégumentaire*.

At the onset of this form of the disease the patient suffers more or less from prodromal symptoms, such as irregular rises of temperature, rigors, lassitude, drowsiness, dyspepsia, diarrhoea, headache, vertigo, epistaxis, and profuse perspiration. These phenomena may be very slight, or they may be in part or altogether absent. Even when well marked they cannot be regarded as characteristic of leprosy; they are such as may precede any specific febrile disease.

As a rule the first positive indication of the disease is the appearance of the leprous eruption, which shews itself as a slightly raised, irregular shiny, erythema-like patch of a reddish or copper tint in white or light coloured races, and of a colour which hardly differs from that of the surrounding skin in negroes and the darker races. There is from the first distinct infiltration of the dermis, and there is usually some hyperaesthesia. The parts which are generally at first affected are the lobes of the ears, the ala of the nose, the malar prominences, the forehead, the eyebrows and root of the nose, the lips and chin. Later the eruption appears on the limbs (especially on the forearms), thighs, and buttocks.

These patches may persist, or some or all may decrease in size, and so



far disappear as to leave the skin at its original level, with only a slight brownish discoloration. In some cases the eruption may vanish altogether giving rise too often to illusory hopes of cure. After a time febrile symptoms again occur, and a fresh crop of eruption breaks out. This may happen several times before the appearance of the characteristic leprous nodules - the so-called "tubercles" - which mark the second stage of the disease. These shew themselves as small papules which gradually enlarge to the size of a pea, or in the course of time even to that of a pigeon's egg. They usually appear first on the site of the former eruption, but they may also arise on parts of the body hitherto unaffected. They are tense, shiny masses, reddish brown in fair subjects, and rather darker than the surrounding skin in the dark races. In the former small blood-vessels may often be seen over the nodule, beneath the tightly stretched integument; and in the latter, whose skins are normally greasy, the openings of the largely developed sebaceous glands are usually evident and plugged with dirt.

In rare cases, a definite primary eruption seems to be absent, one or more nodules being apparently the earliest manifestations of the disease. In one patient, in London, who had come from the West Indies, the first symptom observed was "lameness" in one leg; six years afterwards an eruption appeared on the thigh, and in two years later he was a typical "nodular" leper.

As time goes on, parts of the body free from the original eruption become invaded by the new growths. They appear on the hands and fingers, feet, shoulders, arms, and more rarely on the back, neck, ears, abdomen, palms, and soles. Thickening of the skin on the elbows and knees is not uncommon, but discrete nodules here are rare. The hairy scalp is very rarely affected. The male mammary gland often becomes enlarged and the nipple nodulated. The prepuce also is often thickened and infiltrated by the new growth, and micturition may be impeded. The glans does not usually appear to be affected, Gluck, however, found it infiltrated in ten cases. Loss of hair from the eyebrows is often observed early in the case. The fingers and toes are frequently swollen and tapering without actual nodulation, and the nails break off in flakes. The skin of the shins may become tense, shiny, and painful.

Four distinct varieties of leprous infiltration may in these cases be recognised clinically -

- (a) The original nodules above described may remain discrete, without diffuse infiltration of the skin.
- (b) The nodules may coalesce into large irregular nodose or flatter masses, varying from one to many inches in diameter.
- (c) Diffuse infiltration may occur from thickening of the original leprous patches.
- (d) In rare cases subcutaneous small hard nodules may form, the skin being freely movable over them.

Two or more of the above varieties may co-exist in the same patient. The eye is often involved in this form of leprosy; the conjunctiva



may then be more or less infiltrated, enlarged blood vessels are usually seen, and the new growth may implicate the cornea, extending from the periphery and ultimately penetrating into the anterior chamber. There may be severe pain, and sight may be destroyed. The iris and ciliary body also may become invaded, and even the choroid and retina, the eyeball being thus eventually changed to a shapeless mass, which may increase to such a size that the eyelids cannot cover it. Both eyes are often affected, one after the other.

The mucous membrane of the nose becomes thickened, and sometimes nodules are formed in it, giving rise to snuffling and nasal obstruction. Attention has recently been directed to the frequent early implication of the nasal and pharyngeal mucous membranes in lepers. Nodules and thickenings are occasionally found inside the cheeks and on the palate and fauces, and frequently on the epiglottic, ary epiglottic folds, the vocal cords and ventricles of the larynx. They have been seen occasionally in the trachea and bronchi, the uterus and vagina.<sup>1</sup>

When the nodules are fully developed, the hyperæsthesia which accompanied the initial eruption is replaced by diminished sensation and even by complete anæsthesia, the result of pressure on the ends of the nerves. At this stage also infiltration of the nerve trunks often occurs, the case becoming a "mixed" one.

The further history of the nodules varies. In some cases they remain almost stationary, or increase very slowly; in others they disappear altogether, leaving wrinkled areas of skin, and some persistent anæsthesia, discoloration, or deformity; more commonly they break down, suppurate, and form ulcers.

The face frequently acquires a characteristic leonine aspect, the skin of the forehead being greatly thickened, the natural furrows exaggerated, and the eyebrows prominent, the face then presenting a sombre expression. New growths sometimes form in the eyelids and hang down over the eyes. The cheeks are often puffed out and pendulous from the weight of the exoplasm. In some cases, however, the nodules may remain small and secrete, and cover the nose, lips, and chin as well as other parts of the face. The ears are usually much thickened and nodulated, the lobes being especially liable to infiltration, with consequent enormous enlargement (Fig. 113).

In the largest class of cases the new growths increase very rapidly; fresh crops suddenly appear from time to time, each outburst being accompanied by a rise of temperature to 102° or 103° F. Several such attacks may occur in the course of a year, and during their presence the lymphatic glands, especially the femoral, become painful and swollen. When the fever has passed off, more or less enlargement of the glands may remain. Some recession of the older tubers may be apparent after the attack, but the total amount of leprosy deposit is increased at every exacerbation. The hands and feet often become covered with masses of new growth which are easily injured on movement or by pressure and

<sup>1</sup> Dr. Rake had not seen them in these positions altho' he made many autopsies.

the like; the resulting sores are difficult to heal. The nails drop off and are converted into distorted horny pegs.

The condition of the sexual organs varies. If the disease be developed in males before puberty, the testicles usually remain small and imperfectly developed, and the sexual power is absent: when onset of the disease takes place after puberty, although at first there is



FIG. 113. Nodular Leprosy.  
[An advanced case.]

be increase of sexual desire and power, testicular atrophy and impotence generally follow. In leprosy women there is probably a like effect although by no means always sterile, in most cases they bear few or no children, and their offspring are often, but not always, weak and pale and die early.

After the stage of nodulation has lasted for a variable period the final stage of ulceration sets in, and the growths on the more exposed parts, such as the face, ears, hands and feet, are usually the first to ulcerate

avourable cases, and with proper attention to cleanliness, these ulcers heal and a partial spontaneous cure be established, the patient living years afterwards, much disfigured by irregular areas of cicatricial tissue without any fresh development of nodules. Occasionally, as the result of cicatrization, the mouth becomes so contracted that the tongue cannot protruded, and feeding becomes difficult. Sometimes the ulcers on the hands and hands become the seat of large warty masses.

In other cases the ulcers refuse to heal, and spread till they form irregular tracts of ulceration on the legs, buttocks, forearms, etc.,—sometimes more or less enveloping a limb. Large florid bleeding eruptions often spring up on the ulcerating nodules, especially on the hands and feet. After living for months or years in this state, the patient dies from simple exhaustion, kidney disease, tuberculosis, or other general complications.

In a third class of cases the progress of events is more rapid. The ulcers become phagedænic, especially on the fingers and toes; the gangrene extends, gangrene of one or more extremities follows, and the patient soon dies of exhaustion or pyæmia; but this latter termination is not so common as in the other forms of the disease.

During the course of the cutaneous ulceration just described, other symptoms are often present as the result of ulceration of the mucous membranes. Great pain and photophobia and eventual blindness from corneal opacity follow ulceration of the corneal nodules, even if the latter have not already invaded the rest of the eye. Pain and difficulty in eating and swallowing accompany ulceration of the lips, tongue, and throat, while as the result of the breaking down and cicatrization of the cartilages of the epiglottis and larynx, the voice becomes croaking, and is sometimes reduced to a whisper. The patients also suffer from painful attacks of dyspnoea, which sometimes prove fatal.

*Smooth Leprosy.*—"Anæsthetic," "non-tuberculated," "trophoneurôtic," "atrophic," "neural" or "nerve" leprosy, "Danielssen's disease," *Leprosia*, *L. anæsthetica*, *L. maculo-anæsthetica*, *L. nervorum*, *L. neuroplastica*, *la lèpre systématisée nerveuse*. In the cases in which anæsthesia and trophic changes are the most prominent features the prodromes are less marked than in those just described, and they may be so slight as to be overlooked. Feelings of chilliness, depression, and indefinite malaise are not noticed. The patient may experience shooting pains in nerves, especially the ulnar and peroneal, a burning and tenderness along their course, and hyperæsthesia of the skin of the parts they supply. These symptoms may be absent, and the first evidence of the disease may be the numbness of the hands and feet, and diminished power of grasping. There may be difficulty in holding tools during work, accidental burns and wounds may be quite painless, and walking may feel like treading on

In other cases the maculæ are the first symptoms noticed. These maculæ, which generally appear singly, are of three kinds: (1) those which begin with erythema, (2) those which begin with pigmentation, and (3)

those in which there is a diminution of pigment either initially or rapidly following an excess of the latter. The spots are often of a light copper or brown tint in fair skins, or of a dirty yellow in the blacks, and one or two inches in diameter: they differ as a rule from the primary eruption



FIG. 114. Neural Leprosy.

[An advanced case (said to be of 40 years' duration), showing characteristic deformity of hands and complete peripheral anaesthesia, and paralysis of orbicularis palpebrarum.]

of nodular leprosy in not being raised above the surrounding skin. At this stage they are generally neither hyperæsthetic nor anaesthetic, but the secretion of sweat may be locally absent. The eruption usually appears first on the shoulders, back and loins, buttocks, thighs, knees and elbows and on the face: but the face often escapes altogether. Sometimes it occurs in the areas of certain nerves, such as the musculo-spiral and

ulnar. Fresh patches continue to appear, but the patient's general health may be unaffected—no special symptoms being observed. It often happens, however, that about this time anæsthesia of the skin supplied by the ulnar nerve is apparent; and the fourth and fifth fingers may begin to contract—more commonly in the left hand.

The next stage of the disease is characterised by the spreading of the eruption. After the original spots have remained unchanged for a year or two they begin to enlarge peripherally. The centre fades to a dirty white or pale yellow, and at the same time becomes anæsthetic. The hairs fall out, and the patch becomes wrinkled and dry from the destruction of the sweat-glands. The border is now slightly raised, is of a reddish-brown colour, and may be studded with small papules, which sometimes become vesicular. In rare cases the vesicles increase in size and become pustular. Desquamation is always more or less present as the patch grows, the scales being thin and powdery about the centre, and larger at the periphery. If vesicles or pustules be present, they burst and leave scabs which eventually fall off. Individual spots may increase greatly in size, or neighbouring ones may coalesce into large serpiginously bordered tracts; and immense areas of the integument—for example, the whole of the skin of the back or thighs—may thus become changed. The face is occasionally completely thus invaded and discoloured, the area extending from the margin of the scalp to below the jaw, and imparting to a negro the physiognomy of a half-caste.

The more superficial nerve-trunks may now, or perhaps at an earlier stage, be felt enlarged beneath the skin, especially the ulnar above the elbow. With the spread of the eruption the anæsthesia increases, until in some cases the whole of the upper or lower extremities, or more rarely the greater part of the body and limbs, becomes lost to feeling. Anæsthesia may also be present beyond the area of the patches, even when the latter retain a certain amount of sensation. There are also cases in which there is anæsthesia of the mucous membrane of the mouth and pharynx.

When the active spreading stage is over, the margins of the spots fade in colour and regain the level of the surrounding skin. In white patients it is sometimes difficult to distinguish any difference of colour between the anæsthetic patch and the rest of the skin. In a Frenchman under Dr. Rake's care in Trinidad there was no variation of tint until four years after the onset of the disease: the patches then became mapped out by congestion of the surrounding skin. In very rare cases there may be no skin eruption.

The final stage of permanence is now reached. After the eruption has ceased to be active, or when there is no further deposit in the nerves, the disease may remain stationary for a number of years—the only evidence of the disease being the remains of the eruption, and more or less contraction of the fingers. In the majority of cases, however, paralysis and destruction of tissue progress, as the result of the increased amount of new growth in the nerves.

The contraction which has already been mentioned, as usually com-

mening in the fourth and fifth fingers, extends to the other digits—in less degree, perhaps, in the case of the thumb,—the second and third phalanges being flexed towards the palm, so as to give the extremity a claw-like appearance. The interossei and the muscles of the thenar and hypothenar eminences at the same time become wasted. Similar changes, but less marked as a rule, take place in the lower extremities. As a later effect there may be wrist-drop, and more rarely atrophy of the muscles of the leg, giving rise to a flail-like condition of the foot; and occasionally there is effusion into the wrist and ankle joints, with erosion of cartilage and dislocation of the bones, exactly resembling Charcot's disease. Ulceration frequently now ensues, either as the result of bursting of large bullæ on the hands and feet, or as the effect of mechanical injury to the anæsthetic parts. The patient may take up a hot cup or pipe without feeling it, step on a sharp stone and the like, thus producing wounds which break down into perforating ulcers. More commonly, however, this form of ulcer begins as a bulla which, prevented from early rupture by the thickened epidermis of the sole, burrows deeply into the tissues. Ulcers are especially common on the fingers and toes; and the nails often split and break, or are changed into talon-like appendages.

The bones become necrosed, and are cast off whole or in pieces; or in other cases interstitial absorption of bone takes place, and the finger or toe becomes shortened, the remains of the phalanges ultimately becoming ankylosed. In whatever way the bones be removed, a portion of the nail usually persists as a horny peg attached to the end of the stump. Destruction of the bones of the carpus and metacarpus is rare; but in the lower extremity the necrosis often involves the other bones of the foot as well as the phalanges—especially the metatarsals and calcaneum. Occasionally all the distal parts of both lower and upper limbs are removed in this way, as if amputation had been performed. Rare cases have been described in which the caries has extended beyond the wrist and ankle joints, and the epidermic remains of the digits have been seen even as far up the limb as the elbow-joint.

Ulcers over the knees, shins, elbows, and other parts of the body also occur, but much less frequently than in nodular leprosy; cracks often open on the palmar and plantar aspects of the digits, beginning in the grooves beneath the joints, spreading transversely, and forming chronic ulcers. Suppuration may extend along the sheaths of the tendons, with resulting necrosis of the latter as well as of the bones. In other cases a furrow may form between the joints, and by gradual deepening produce a condition resembling ainhum. Though the ulcers of "anæsthetic" leprosy are for the most part painless, distressing neuralgia may accompany perforating ulcers of the foot; and in other cases there may be intense pain in the sciatic, ulnar, supraorbital, and other nerves, due to the interstitial deposit. The patient, moreover, often complains of feeling cold. The ulcerations sometimes spread rapidly, and become gangrenous, all the tissues being affected, and a line of



demarcation formed. The gangrene may be limited to one or more of the fingers or toes, or the whole hand or foot may be involved; in rare cases it may extend farther up the limb. As a result of hard labour, handling tools, etc., suppuration may be set up in an anæsthetic finger, and may travel up the tendons and burrow into the muscles as far as the elbow. Towards the end of life symmetrical bed-sores sometimes form rapidly over the buttocks.

The affections of the eye in this form of leprosy are mainly the result of lesions of the fifth and seventh nerves. Ophthalmia is not uncommon, and ulceration of the cornea frequently occurs which may lead to pannus, onyx, hypopyon, iritis, and occasionally to the destruction of the whole eye. There may be ptosis; and paralytic ectropion is often seen, with facial paralysis of the same side. The surface of the cornea may be quite anæsthetic without any of the other evidences of disease.

Sexual desire is not as a rule increased in smooth leprosy; but the power of procreation is retained until a comparatively late period.

"Mixed" Leprosy. Gerlach and others believe that in the smooth form of leprosy the primary growth commences in the integument around the peripheral nerve endings, travelling up along the fibres, so that, in one sense, even these cases are "mixed" from a very early period. It is nevertheless true, that in the majority of cases the early skin changes do not, as we have seen, present quite the same appearances as in nodular leprosy.<sup>1</sup> In a large number anæsthetic patches and other evidences of nerve infiltration co-exist with definite cutaneous thickenings, and we may therefore, for clinical purposes, class such cases together under the appellation of "mixed leprosy." These may also be considered under three heads—

(1) Those in which the leprosy infiltration is for a long period confined to the skin, and subsequently advances to the nerve-trunks.

(2) Those in which the symptoms of nerve implication are for a considerable time manifested alone, the formation of dermal nodules being subsequent; and

(3) Those in which the leprosy dermal infiltrations and the various symptoms of nerve-trunk implication are observed together from a very early period of the disease.

Of these the first class is by far the most numerous, and, indeed, so often do the nerve-trunks become involved in advanced cases of nodular leprosy, that we may regard a leper with this latter form of the disease as one who has not lived long enough to develop "mixed leprosy," which is the complete or generalised affection.

The second class of cases, in which nodules develop late in the course of neural leprosy, is undoubtedly rare. In ten years' experience at Trinidad only three instances were noticed. Leloir also only mentions three cases.

The third class is less uncommon, and it often happens that early

<sup>1</sup> Hansen does not recognise this distinction, although he admits that the patches of the tuberculous form are certainly usually thicker, indicating a greater degree of infiltration than the anæsthetic.

cutaneous infiltrations almost or quite disappear, there remaining only anæsthesia, deformity, etc. In such cases it would sometimes be difficult to believe that the patient's skin had ever been nodulated were it not for



FIG. 115. Mixed Leprosy.

[An early case of one year's duration. The anæsthetic patches were raised and reddish in the centre with surrounding leucodermic areas. The patient has subsequently developed nodules on the face.]

the presence of flabby, wrinkled patches on the ears, cheeks, and other sites of the former nodules. A detailed account of the symptoms of "mixed" leprosy is unnecessary, for they consist of a combination, in varying proportions, of the phenomena already described.

In the Trinidad Asylum, during a period of eight years, pulmonary and other forms of visceral tuberculosis were immediately responsible for 20 per cent of the deaths among the nodular cases, for 19 per cent of the deaths among smooth cases, and 25 per cent of those among the "mixed" cases; various forms of kidney disease caused 30 per cent of the deaths among the nodular cases, 27 per cent among the smooth, and 10 per cent among the mixed; tuberculosis and renal affections combined were responsible for 14 per cent, 3 per cent, and 10 per cent of the deaths respectively; and the leprosy itself, or exhaustion from leprosy ulcerations, gangrene, pyæmia, asphyxia, due to obstruction of the larynx, and accidental complications, were ascribed as immediate causes of death in 36 per cent of the nodular, 51 of the smooth, and 55 of the mixed lepers. Observations in the same asylum extending over 18 years shewed the average age of onset to be  $21\frac{1}{2}$  years,  $30\frac{1}{2}$  years, and  $25\frac{1}{2}$  years in the three classes of cases respectively.

**The Diagnosis.**—When nodular leprosy is fully developed its diagnosis should be a matter of no difficulty; for apart from the obvious naked-eye appearances—the localised nodulations, thickenings, and discolorations, the history of the primary eruptions, etc.—a small piece of new growth excised or scraped will always exhibit the specific bacilli. In an early stage the eruption might be mistaken for a syphilide, but microscopical examination, the test of antisyphilitic treatment, and careful consideration of concurrent symptoms—as well as the history—should soon settle the matter. The characters of the primary eruptions, already described, the special sites of predilection, the far more chronic course, and the accompanying local loss of hair, sufficiently distinguish the leprosy from the syphilitic exanthem. It must not be forgotten that syphilis may co-exist with leprosy; its characteristic lesions should therefore be looked for.

Certain cases of tuberculides—*lupus vulgaris*, *scrofuloderma*, as well as *L. erythematous*—have at times been mistaken for leprosy; but the history and other characteristics should suffice to distinguish the diseases, even without an examination for the bacilli. The same also may be said of the idiopathic erythemas which may resemble the first stage of the leprosy eruption, especially *erythema exudativum*, in which the patches are smaller, run a more acute course, clear up from the centre as they increase in size, and leave but a transitory stain; there is, moreover, not the same notable alteration of sensation or febrile disturbance.

Many other diseases causing tumefactions of the skin have from time to time been mistaken for nodular leprosy—for instance, pigmented sarcoma and other malignant growths, elephantiasis arabum, molluscum fibrosum, yaws, acne—but attention to the above descriptions should leave no doubt in the mind of the observer.

On the other hand, it is not always so easy to distinguish cases of purely neural leprosy from certain other affections in which the nervous system may be implicated. Advanced cases have frequently been confounded with syringomyelia, Morvan's analgesic whitlow, progressive muscular atrophy, peripheral neuritis, sclerodactyly, anhidrosis, and Ray

naud's disease. The resemblance of these diseases to certain cases of this form of leprosy is, indeed, so great that Zambaco Pacha has unhesitatingly affirmed that they are all of them, as well as scleroderma and morphea, modified or attenuated forms of leprosy. As a general rule, however, the sufferer from neural leprosy exhibits at some stage the characteristic discoloured and anæsthetic patches on the skin, and he has almost invariably been in leprosy districts or has associated with lepers. Moreover, the bacillus may be found sooner or later in the neoplasm in the nerves.

The eruption in the early stages may sometimes closely simulate leucoderma; and in children especially, or in patients of weak intellect, the diagnosis may be retarded by the difficulty of determining degrees of anæsthesia.

It has been estimated that at least 5 per cent of the supposed lepers in the East are suffering from other diseases which superficially resemble true leprosy.

**Prognosis.** The prognosis in leprosy is very bad. It has been said "once a leper always a leper," and that the disease is incurable. It is true that with very few exceptions the malady goes on from bad to worse in spite of all treatment, and that the patient's life is shortened. Yet it must be remembered that in many asylums in Norway, and elsewhere, there are inmates in whom the disease has been arrested for many years—the cases practically cured, but of course with more or less deformity and loss of tissue.

Several instances of apparent cure have been recorded by Munro, Hutchinson, Cottle, Unna, Philbppo, C' Fox, Francis, the Norwegian physicians, and others, and in some of them, at any rate, a recrudescence of the disease had not appeared up to the time of the death of the patient in old age. The official report for Norway gives the number of cured cases at thirty-eight during the five years 1881 to 1885. There is, indeed, reason to believe that there is hope in some cases, especially if measures be adopted at an early stage. The disease occasionally proves fatal in a year or two, or it may progress more slowly, especially when the nerves only are affected, for several decades. Lepers are occasionally seen in whom the disease has been slowly progressing for forty years. Observations at Trinidad gave in 18 years an average duration of life of  $6\frac{1}{2}$  years for the nodular, 10 years for the neural, and  $9\frac{1}{2}$  years for the "mixed" cases. These figures seem worse than those given by Danielsen and Boreck—namely,  $9\frac{1}{2}$  years in the nodular, and 18½ in the neural form; but those observers excluded all deaths from intercurrent diseases. Carter's calculations for Bombay approximate to the Norwegian statistics; and Leloir gives 8 to 12 years for nodular cases, and 18 to 20 for the neural. When the affection makes its appearance in early life, its course, especially in the neural form, is usually more rapid than when it attacks old people, and frequent outbreaks of nodules, and early implication of the larynx, make the prognosis more unfavourable. The progress of the disease is usually

in cases with diffuse infiltrations of the skin than in those in which groups of discrete nodules frequently appear. The presence of complications shortens the expectation of life in all cases of

**Treatment** of leprosy is by no means satisfactory ; but although a complete cure can rarely be anticipated, it is a mistake to suppose that nothing can be done to prolong life, or to mitigate suffering, or even to eradicate the disease. We may consider the treatment under three heads Hygienic, Medicinal, and Surgical.

**Hygienic.**—It is of the utmost importance to lepers, as to others, that their surroundings should be healthy. They should have plenty of fresh air, their dwellings be well ventilated and dry, the influence of heat and cold avoided, strict cleanliness enforced, and good, nourishing diet provided, such as fresh meat and vegetables, with no indigestible food. Fish and other decomposable substances should not be eaten unless quite fresh. Some few lepers have stated that their ulcers have become worse after eating fish ; but this is by no means the general experience. Plenty of exercise should be taken, as to promote the general nutrition as to excite, if possible, the action of the sweat-glands. The patients should be warmly clothed, for they are usually very susceptible to cold ; and we have seen how liable they are to disease of the kidneys.

Removal to another climate, especially to a country in which the disease is not endemic, often has a very beneficial effect, particularly in the advanced stages of the disease. Many colonials, for instance, who have lived in the uninfected parts of Europe have probably lived longer than they have done in their own countries.<sup>1</sup>

**Medicinal.**—No specific drug has yet been discovered for leprosy, but it must be admitted that effects, both locally and generally, can often be produced by certain external and internal remedies. In estimating their value in individual cases, however, it must not be forgotten that the symptoms of the disease are sometimes modified, or even arrested for a considerable time, spontaneously or by improved hygienic conditions alone.

Among the numerous vegetable oils which have been used for leprosy, cod-liver-oil, or "chaulmoogra oil," appears to be the most

valuable. A case is known to me. Ten or twelve years ago a gentleman, then aged about 40 (a married man, by the way), who had suffered a good deal of privation as a soldier in the East, consulted me for numbness and pains. The ulnar and other nerves were easily traceable by the finger for long distances on both hands, and there were numerous patches. At my request he consulted an eminent authority on leprosy, whom I had previously warned to give the diagnosis to me only. He agreed with me that the case was an early but well-marked leprosy. To the patient's surprise, we made him throw up his hands and forbade him to return to the East in any circumstances. He is now well and ignorant of his malady ; I have not examined him for some years, as he has been content to be well, and it is best for him not to have his attention drawn to himself. Twenty-five or thirty years ago a young medical man shewed me his own fingers, the ulnar sides of the hands, were contracted and anæsthetic. He was born in India, and took leprosy as a child. He had lived in England since childhood, and considered himself to be quite "cured."—T.C.A.

efficacious, and it is certainly believed in by the lepers themselves. At the Trinidad Asylum, in eighteen cases in which its prolonged use was tried, the chief effects observed were—(1) Increase of perspiration, (2) decrease of the nodules, (3) improved appetite, (4) lessening of anæsthesia, (5) greater suppleness of the skin, (6) lessening of the pains in the joints. The oil may be given in doses of 10 minims, preferably in capsules, two or three times a day, and gradually increased until one or two drachms are taken in the twenty-four hours. At the same time it should be well rubbed in—either pure or as an emulsion with an equal part of lime water—twice a day over the affected parts of the skin, or even over the whole body. The active principle of the oil, gynecardic acid, has also been prescribed internally by Besnier and others. The soda and magnesium salts are well borne, and in at least two cases in England under my own care they have appeared, in combination with external treatment, to be of distinct benefit. Satisfactory results have been obtained by the intramuscular and subcutaneous injection of this oil (Tourtoulis Bey). Gurjon oil, which is used internally and externally in the same doses and manner as the chaulmoogra, has not seemed at Trinidad to be so useful. It is possible that the good results originally obtained by Dougall in the Andaman Islands were in part due to the fact that the patients, being convicts, were compelled to inunct themselves in a most thorough manner twice a day for two hours each time. Hillis speaks well of the gurjun-oil treatment. Others have not been equally successful with these oils, and the failures may have been due to the difficulty of carrying out methods of treatment so prolonged, troublesome, and disagreeable; and also to the varying compositions of different specimens. Phillippo of Jamaica has brought forward a case of well-marked leprosy of six or seven years' duration, which he treated vigorously with gurjun oil externally and chaulmoogra internally from 1879 to 1886. The man during that time practically "lived" in great improvement gradually set in after the first two years of the treatment, and at the end of the period all the symptoms had disappeared. He had remained "cured" for five years when the account was published in 1890.

It has been suggested that the persistent and thorough application of any oil may ameliorate leprosy; and good results have been especially claimed for the cowti oil advocated by Bhao Daji of Bombay. The latter oil has not, however, proved so useful as chaulmoogra in the experience of other physicians.

The Beauperthuy treatment, which has been much lauded, consisted in applying cashew-nut oil, as a local caustic, to the nodules and patches, prescribing at the same time careful diet, attention to the functions of the skin by frequent friction and baths, and other hygienic measures, as well as internal medication with alkaline salts or perchloride of mercury. The cases which were reported as cured, however, subsequently relapsed. Mercury, although extensively tried, has been of little or no therapeutic value in leprosy, except when complicated with syphilis. Dr. Radcliffe



r has reported good results in two cases from intramuscular injections of perchloride of mercury. This method was tried in many at Little Bay Asylum, New South Wales, without modification of course of the disease.

In some cases at Trinidad arsenic was beneficial. It was administered as the liquor arsenicalis, commencing with three minims and gradually increasing the dose until the limit of toleration was reached. In some cases there was a marked diminution of the febrile nodular eruptions. This drug has also been employed in leprosy by Mr. Manson and others.

The supposed specific of the Chinese, "Hoang Nan," has proved of no use in Hawaii, India, and elsewhere.

W. J. H. Nielssen obtained better results in leprosy with salicylate of soda than with any other drug. When indicated he also gave cod-liver oil, quinine.

W. J. H. T. reported good results from the administration of salol in large doses, 20 to 30 grains three times a day, and Cook in Madras also obtained a temporary mitigating effect from its use; but the latter came ultimately to the conclusion, after a three months' trial in twelve cases, that salol has really no therapeutic value in leprosy.

For reducing remedies, ichthyol, resorcin, pyrogallol, and chrysarobin have been strongly recommended by Unna, who has published of supposed "cure" by their use. Many observers have, however, found that, although local improvement may be effected by these means, they have not justified expectations. A similar remark may be made with regard to eucrophen, which Goldschmidt found useful in one case in Australia. The local application of formalin is recommended by Manson.

Potassium chlorate was given in large doses by Caneau to a leper in Martinique, who took 675 grains in three days, with distinct diminution of the nodules. It was tried on two patients at the Trinidad Asylum in doses amounting to 80 to 100 grains a day for several weeks. Only a slight decrease of the nodules was noticed, probably not more than could have been effected by free purging with magnesium salts.

The injection of tuberculin has been shewn to be practically valueless in leprosy by a considerable number of observers, including myself. Constitutional disturbance is as a rule produced, but of a somewhat different character from that caused in tuberculous patients, and some of the nodules may soften and disappear. Fresh ones, however, crop up, and patients are generally no better off after the treatment than before.

They have administered thyroid gland to two patients in England, and in both the effect was apparently good; the man felt better in every way after taking the tablets for about a year, and had no febrile attacks; there seemed also to be some lessening of the cutaneous induration. In the second case it was tried for a few weeks on five patients with well-developed leprosy, with but little effect. In most of them the symptoms of thyroidism were produced.

The inoculation of erysipelas in one case has had a good result, but the treatment is dangerous, to say the least of it.

Experiments in connexion with blood-serum therapy have been tried at the Trinidad Asylum and elsewhere, in the anticipation that a specific antitoxin may be discovered for leprosy.

Carrasquilla injected the blood of lepers into horses and subsequently injected the horse-serum into a large number of lepers at Bogota, and published most encouraging results. His serum has been widely tried in other countries, but with little or no good effect. Herman and myself, in 1896-7, employed in two cases in London a serum obtained from a horse into whose jugular vein an emulsion of leper-juice from recent nodules had been introduced. There was an apparent beneficial effect in one of the cases. A sample of the same serum was sent to Robben Island and used by Atherstone and Black in two cases; they reported that some improvement was manifest in one of them, an anæsthetic patient. Many experiments in this direction are now in progress with hopeful anticipations. Dyer, in New Orleans, has had good results by injecting in several cases antivenene prepared from snake poison. Capt. Rost has prepared a "leprolin," on the lines of Koch's tuberculin, from supposed cultures of leprosy bacilli, and has reported good results from its use in a large number of cases. Wood and Fleming, and several other medical officers in India, have tried Rost's preparation with more or less improvement in the symptoms of the disease. In all cases Capt. Rost recommends an accompanying local application of common salt.

*Radiotherapy and Electricity.*—Under the influence of X-rays discoloured patches and nodules often diminish and sometimes disappear. I have seen this also take place under radium. In the case of the patient whose arm is figured (Fig. 115), marked improvement followed a course of high-frequency electricity applied to the arm, sensation and considerable power returning in the hand and digits.

*Surgical.*—Surgery can do much for lepers; and operations, when indicated, may be performed upon them without hesitation. Their tissues indeed heal with rapidity, in consequence, it is believed, of the excess of fibrin-factors which, as shewn by Daniëlssen and Boeck, Hillairet and Rake, is contained in their blood. The mean percentage of fibrin obtained from leprous blood at Trinidad in fifty observations was found to be 0.76.

Amputation of a useless and encumbering member is sometimes advisable, especially in cases of gangrene. Nerve-stretching has frequently been of service in combating the intense pain which may result from the neuritis; indeed, the healing of perforating ulcers may be thus promoted, and improved sensation may follow the operation. Of 100 stretchings at the Trinidad Asylum more or less relief was experienced in forty-seven. Cols. Macleod, Lawrie, Downes, and others in India have employed nerve-stretching with much benefit; and Col. Macleod also recommended "nerve-splitting." The best treatment for perforating ulcers

of the sole was found at Trinidad to consist in passing a bistoury right through to the dorsum of the foot, and thence cutting or splitting all the tissues forward to a point between the toes; the wound is then allowed to granulate.

Dead bone should always be removed when practicable, and thus gangrene may often be arrested. Sinuses should be slit open, and ulcers freely incised down to the bone. Iodoform, carbolic acid, or other antiseptic substances and dressings should be used.

Cutaneous nodules may be freely excised, especially when they cause obstruction, as on the eyelids, prepuce, etc.; and according to some observers they do not return. Free incisions are often of service in relieving the hide-bound condition associated with leprosy infiltration of the skin, and in obstructing the nutrition of the new growth.

When the new growth is invading the cornea, iridectomy, performed before the iris is infiltrated or adherent, may preserve some vision for a time. Boeckmann and Kaurin have found keratotomy sometimes of use in saving a cornea from a growth encroaching from the sclerotic. Trachelorrhaphy is also occasionally indicated for the paralytic ectropion.

Tracheotomy frequently prolongs life in leprosy, and there are lepers going about in the various asylums in Norway who have worn the tube for many years. When the larynx becomes invaded, and dyspnoea is threatened, the operation should be performed.

**The Prophylaxis of Leprosy.**—If we grant (1) that leprosy is due to the presence of a specific bacillus, (2) that the habitat of this organism is the human body, and (3) that the parasite may pass from one host to another, it follows that the most radical prophylactic measure against leprosy is the total avoidance of all contact with lepers, with anything that may come from their bodies, or with anything that they may touch. We have seen, however, that practically the contagiousness of leprosy, if it exist, is comparatively slight, that its inoculation is extremely difficult to bring about, and that it is a somewhat rare event for persons in association with lepers ever to contract the disease. Nevertheless, even though the risk be small, it should be borne in mind; and people who have to live in leprosy countries, and who may sooner or later, knowingly or unknowingly, come under the influence of the contagium, such as it is, are well advised in avoiding close contiguity with lepers, in preventing the latter from handling food, utensils, clothing, and the like, which the healthy have to use, and generally in adopting all common sense sanitary precautions. Medical men and attendants particularly should be careful; and, if there be abrasions or cuts on their hands, they should abstain from touching the lepers until their wounds be healed, at other times after tending their patients they should wash their hands with antiseptics.

Indeed, similar prophylactic measures may be taken as against tuberculosis and syphilis, although both of these diseases, it is needless to say, are far more readily communicable than leprosy.

*The question of Compulsory Segregation.* A great many sanitary authorities recommend the absolute isolation and segregation of all lepers; but

although, theoretically, such a measure might be expected in time to eradicate the disease from an infected country, a number of valid arguments may be adduced to shew that it is hardly practicable or even advisable in many places. It has been alleged over and over again that it was in consequence of the stringent laws of the Middle Ages that leprosy was stamped out in many districts, and also that the isolation of lepers in Norway is causing the diminution of the disease in that country. That these attempts at isolation and segregation may have had something to do with such results need not be denied; it is practically admitted above that every leper may be regarded as a breeder and carrier of the bacilli, and thereby as a possible focus for the dissemination of the disease; but real isolation has never been complete, and is never likely to be. Even in the olden times it is well known that wealthy and powerful persons afflicted with leprosy managed to escape the pains and penalties and to avoid incarceration, and there must have been many of all classes secreted by their friends; as we have seen, too, lepers were always allowed to wander about and beg. The diagnosis in those days moreover, was by no means certain, and there can be no doubt that lepers in the early stages of their disease were more frequently overlooked even than now.

In Norway there never has been any attempt at complete segregation. It is true that in 1856 there were nearly 3000 lepers altogether in that country, and that at the present time there are certainly less than 500; but the number of the inmates in all the asylums put together never at any time exceeded 800, and that number has been gradually diminishing in the last thirty-five years (*vide* footnote on p. 651). Until a few years ago, indeed, entrance into the asylums was not enforced, even in the case of indigent lepers; but in 1885 a law was passed to compel those to enter who could not be "isolated" at home; that is, who could not arrange in their own homes for a separate bed, separate clothes, separate utensils, and so forth. Indeed, the isolation and segregation of lepers in Norway is, even now, only partial; and in 1888 I found that the patients were frequently allowed to leave the hospitals and walk about the neighbouring roads. The individually so-called "isolated" patients throughout the country must of course have even greater freedom.

It must be admitted, however, that it is only since these measures incomplete though they be, have been adopted that leprosy in Norway has actually declined; although this decline may have been also favoured by the improved sanitation, better food, and increased prosperity of the people. Hansen believes that in 1920 "there will be no more leprosy in Norway."

Ehlers has shewn that the recent more stringent segregation of the lepers of Iceland, and the education of the people in reference to its communicability, have been accompanied by a marked diminution of leprosy in that island—in five years from 200 to 133—and that within the same period there has been no material change in the habits or food of the inhabitants.

In the Sandwich Islands, on the other hand, most determined endeavours have been made since 1865 to segregate the lepers completely ; but the efforts have certainly not met with the success anticipated, either in the discovery of all the lepers or in the marked diminution of the disease throughout the country. Numbers of affected persons, to evade separation from their families, have been secreted ; and in spite of the stringent laws leprosy went on steadily increasing in the islands until 1890 at any rate, since which date a slight decrease has been noted. The ultimate success of the Hawaiian segregation remains yet to be seen.

In reference to this question the following conclusions were adopted at the "International Leprosy Conference" in Berlin in 1897 :—

1. In countries where leprosy forms foci or has a great extension, isolation is the best means of preventing the spread of the disease.

2. The system of obligatory notification, of observation and isolation as carried out in Norway, is recommended to all nations with local self-government and a sufficient number of physicians.

3. It should be left to the legal authorities, after consultation with the medical authorities, to take such measures as are applicable to the local social conditions of the districts.

In most countries, indeed, where leprosy exists on a large scale, it may be taken for granted that a harsh measure of complete compulsory segregation is impracticable ; but legislation, somewhat on the Norwegian lines, might very well be adopted in all places where the disease is endemic. In such countries lepers should be prevented from freely mixing with other people ; from carrying on any occupation which may bring them into contact with the healthy, or any trade connected with food, clothing, and the like. Unless they can be maintained in their own homes with proper sanitary precautions, they should be treated in special hospitals, and mendicant lepers should be secluded in suitable institutions. In India and similar places the establishment of leper farms or colonies might be encouraged after the plans which are said to work so well in Cyprus and at Sialcote ; and although matrimony and sexual intercourse should obviously be discouraged, there is no need to add further to the miseries of their existence by separating husband and wife, or even, in some cases, by prohibiting the marriage of lepers ; for, as we have seen, the prospect of their procreating children is comparatively small. Any children born in such settlements should be brought up in separate orphanages.

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## YAWS

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**ONYMS.**—The name Framboesia was originally given to this disease by Sauvages in 1759, from the French word *framboise*, a raspberry, because of the resemblance of the characteristic growths on the skin to that fruit. In the West Indies the colloquial name for it is *yaws*, possibly from the native word meaning a strawberry.<sup>1</sup> Similarly, in the French Antilles it is called *pian*; in the Brazils, *boba*; on the West African coast, *gattu*, *dubé*, and *tangara*; in the Moluccas, *bouton d'amboine*; in Fiji, *coko*; in New Caledonia and the Samoan Islands, *tonga* or *tono*; in Ceylon, *parangi*; and in South Africa among the Basutos, *makaola*.

**ort Description.**—A chronic, specific, and contagious disease, characterised by an eruption of raspberry-like tubercles, usually accompanied more or less constitutional disturbance, and tending slowly to spontaneous cure.

**Distribution.**—Yaws is essentially a disease of tropical climates, being found chiefly in Dominica and Jamaica in the West Indies; on the East Coast of Africa for about 10° on each side of the Equator; in Madagascar and Mozambique; in Oceania, chiefly in Fiji, New Caledonia, and Samoa; in tropical South America; in China, Ceylon, Java, and Sumatra; and less commonly in Assam and some parts of India and North Africa.

**History.**—Although Ali Abbas, an Arabian physician writing in 977, mentions a disease under the name of "safat," which may possibly have been yaws, our first reliable accounts of the affection are by Oviedo, who met with it in St. Domingo, and writes of it under the name "bubas." Subsequently, in the seventeenth century, we find various medical accounts of it from the Brazils and the West Indies, by Piso, Bontius, and Labat; a hundred years later, Sauvages recalled attention to it in his classical work *Nosologia methodica*. It is, however, chiefly to Gavin Milroy, Murray, Bowerbank, Macgregor, Charlouis, Kynsey, and other writers of the last thirty years, that we owe most of our present knowledge of it. As in the case of most other diseases, we have no very precise knowledge how this peculiar affection originated; but sufficient is known to justify our belief that, so far as its prevalence in the West Indies is concerned, the original habitat of yaws was the West Coast of Africa, whence it spread by the exportation of negro slaves to the Spanish Indies. On the other hand, there is evidence to shew that, notwithstanding an extensive negro immigration, many regions of the

<sup>1</sup> Nicholls has suggested that the Celtic word *ias*, pronounced *yas*, and meaning heat, boiling, or bubbling up, is the true source of the English derivation of the name yaws.

tropics have been free from yaws; and that it has raged in the past, or exists now in other parts of the world, such as Polynesia, whither no importation of negroes has taken place.

During the period of slavery the disease appears to have prevailed with some virulence in the West Indies, where special means had to be adopted for the isolation and treatment of those affected. In some islands, notably in Dominica, after the abolition of slavery the disease largely increased, owing apparently to the lessened supervision which the authorities were able to exercise over the housing and general condition of the negroes. In Jamaica, on the other hand, Bowerbank relates that a diminution took place after the emancipation; this he attributed to the cessation of the practice of inoculation which previously had been prevalent among negroes. In recent years several recrudescences of the disease have taken place, while Antigua and Barbadoes are now practically free from the affection. It is still met with on the West African coast, and was observed in Assam in 1896.

**Etiology.**—Yaws is, as I have said, essentially a disease of the tropics; though possibly the “morula,” or button-scurvy of Ireland (now extinct, but described by Wallace, Corrigan, and other writers, from 1823 to 1851, as a contagious disease prevalent in the south and interior of that island), was closely allied to if not identical with it. Neither sex nor age is exempt from yaws, but it is most common in children from one to fifteen years of age. Race has a disposing influence, as negroes are peculiarly liable to it; mulattoes, creoles, and pure whites are less susceptible. There is much reason to think that the comparative immunity of the latter is because they are less often exposed to contagion. There is little or no evidence to shew that either any particular form of *diet* or *heredity* has any special effect on the causation of the disease. What part heredity plays in the extension of frambœsia is difficult to appraise, but it is beyond dispute that children are never born suffering from yaws. It is common enough in young children, but only when there have been opportunities for contact. For some statistics on this point Dr. Rat’s work should be consulted.

The negroes of the West Indies universally believe that one attack protects against another, and no doubt, as a rule, frambœsia is not contracted twice; but cases are not rare in which a second infection has followed a first attack. This, however, is not opposed to our experience in other specific diseases, such as scarlet fever and small-pox. Macgregor says that, in Fiji, the notion prevails that unless a child suffer from *cabo* he will not grow up to be a healthy adult; to attain this end, children are either inoculated with the disease or sent to live in the same hut with persons already suffering from it.

Considerable importance has been attached in the past to insanitary conditions of life among negroes and other native populations; but these have only an indirect influence, certainly aggravating the type of the disease, and favouring its dissemination, but not producing it.

That frambœsia is contagious is undoubted. Every one who has had

any experience of the disease in its endemic centres knows that the affection spreads by contact, and that it is rare to meet with a case where a pre-existent case could not be traced in the immediate surroundings of the patient. It is inoculable through an abrasion or sore, but not through the unbroken cuticle. Ulcers on the foot or leg are common points of entrance for the virus in negroes. It attacks only those living in contact with the diseased. The uncleanly are more liable to attack than the cleanly ; but healthy and cleanly alike take the disease if they be brought into direct contact with the infected. Thus, it may be transmitted by sexual intercourse, or from a child to its suckling mother, and conversely. The common house-fly is believed frequently to be the vehicle of contagion ; similarly, transmission of the disease may follow wearing the clothes or sleeping on the mat of an affected person, or even the suctorial acts of ticks and other parasitic insects. The disease does not seem to be often contracted otherwise than by positive contact of the healthy with the diseased ; and aerial infection is practically non-existent. This latter fact is shewn by the experiences of those attending the sick in the yaws hospitals, where, so long as the nurses are cleanly and are careful not to abrade the skin, they do not contract the affection. Keelan's experiences in Dominica suggest that vaccination mitigates or prevents framboesia. He found that of the greater number of cases of the disease which came under his notice, very few were vaccinated, and that the few who had been vaccinated were attacked mildly. This apparently favourable connexion between framboesia and vaccination has not been corroborated by other physicians.

Of interest in relation to the etiology of the disease is the observation that fowls suffer from tubercles on the head and parts not well protected by feathers, which closely resemble those seen in man afflicted with framboesia. Hitherto, in spite of several attempts to transmit the human disease to fowls and animals, no trustworthy evidence has been brought forward to shew that this affection of fowls is either inoculable, or that it is identical with yaws in man. The general view, among competent observers, is that the affection in fowls is really molluscum contagiosum, and quite distinct from framboesia. In this connexion, it is interesting that a spirochætal affection is known to exist in fowls, and that Marchoux has shewn that it is transmitted from one bird to another by means of a tick, *Argas miniatus* (vide p. 194). We know that spirochætæ are present in certain cases of yaws, and, in view of the remarkable developments in recent years of the part played by insects in the dissemination of protozoan diseases, it seems advisable to keep an open mind as to the possible relation between the human affection and that of fowls.

**Pathology.** — Framboesia tubercles present no very characteristic histological features. When examined they appear to be composed essentially of granulation-tissue, which represents a dermatitis confined mainly to the papillary layer, extending more or less into the corium and invading the skin-glands and hair-follicles. The epidermis is usually detached, and the rete infiltrated with leucocytes. The exciting cause



of these inflammatory changes is undoubtedly a specific infective virus. Pierrez describes a micrococcus, obtained from tubercles of frambœsia, which he is disposed to regard as the exciting organism; but he has not shewn that a disease, identical with frambœsia, results in an animal inoculated with a pure culture of this micrococcus. Apparently the same micrococcus has been constantly found by Nicholls in the secretions from the granulomas characteristic of yaws, and also in abundance in the tissues of persons suffering from the disease, no other pathogenetic microbe being found in association with it. In no instance was this micro-organism discovered in the blood, although it has been successfully cultivated in serum. Pure cultures of this micrococcus of yaws show that its microscopical characters are constant, and that its macroscopical reactions differ from those of all other micrococci. The lower animals are probably immune, inoculations giving negative results, as does likewise inoculation with secretions from the granuloma. In the absence of the conclusive proofs of the pathogenesis of this microbe—namely, the production of the disease in healthy animals, and the after-discovery of the micro-organism in the fluids or tissues—it cannot be supposed that the microbe is the contagium of the disease; on the contrary, it may be regarded as one of the many saprophytes common in the secretions of ulcerated surfaces. Dr. Castellani's observation as to the presence of spirochætæ (*vide* p. 46) requires confirmation, and further information is necessary as to the constancy with which these protozoa are present in frambœsial tissues. What little is known at present points strongly to the view that they have a direct bearing upon the causation of these lesions.

**Symptoms.**—There are practically four stages in this disease: First, one of incubation, lasting from two to seven weeks without any very special symptoms; second, a period marked by a febrile condition which lasts from two to eight days, terminating usually with the appearance of an eruption; third, a period marked by successive crops of the eruption, which may last from a few months to two years; and, fourth, a lengthened period of sequels, often extending over five or seven years.

The *incubation-period* is difficult to determine, and has been variously stated by different observers. Paulet, who inoculated healthy negroes with yaws fluid, puts it down from ten to twenty days; but extensive clinical experience indicates that it varies from a fortnight to two months.

**Premonitory Stage.**—During this period there may be no disturbance of health; but not infrequently there are vague pains in the limbs, palpitation, indigestion, and even fever. These constitutional disturbances are usually more marked in children than in adults. In negroes the skin commonly loses its lustre, becoming scaly and often lighter in colour. These symptoms often remit before the appearance of the eruption, which occurs in from seven to ten days, and is preceded by enlargement and tenderness of the lymphatic glands. At this time, if a case be closely examined, the seat of inoculation may perhaps be discovered as a minute papule exuding a pale yellow fluid, or even as a very slight growth of



anulation-tissue. But more commonly, in spite of careful search, no sign indicative of the point of entrance of the poison is to be found. By chance the virus of yaws happen to have gained access to the body through an existing ulcer, this will be noticed to have retrograded and become unhealthy-looking.

*Eruptive Stage.*—The eruption makes its appearance as a small papule, usually, but not necessarily, on the scar of an old wound or sore, giving clue to the seat of inoculation. More often it consists of slightly elevated papules about the size of a pin's head, single or scattered over the body, and having a broad base; if situated on the lips it looks like a commencing herpes. In a few days the papules enlarge, forming tubercles varying from a quarter of an inch to two inches in diameter. As the papule increases the epidermis splits or cracks, exposing a raw papillary surface from which oozes a yellowish white sero-purulent fluid. Unless irritated these tubercles do not resemble the raspberry. The yaws are usually circular in form, and all sizes may be met with on the same patient, varying from a pin's head to that of a golf-ball or even larger, and in every stage of progress. Generally they are discrete; but sometimes they occur in groups, or arranged in a circle enclosing healthy skin. This variety is sometimes spoken of as "ringworm yaws."

Imray has described two unusual forms of the eruption. In one the tubercles are replaced by circular scurfy areas of different sizes. These are known, among the negroes, as *dartres*, and are very persistent and rebellious to treatment. The other variety appears as small, slightly prominent vesicles distributed over the body, called *pian grutelle*; they frequently follow an ordinary eruption of yaws, and are also very difficult to cure.

When the disease attacks the soles of the feet or the palms of the hands it is called *tubbæ* or "crab yaws." The epidermis being usually very thick in these situations the yaws are unable to expand, and thus give rise to much pain. When they do break through, the resulting growth is often small, but secretes an abundant serous fluid. Sometimes these cases present a honeycombed appearance from the excess of exudation and the thickening of the cuticle around the openings.

In some rare instances one of the frambœsia tubercles may assume very large proportions—one or two inches in diameter—projecting from the skin like the other yaws, and covered with yellow scabs. Such a tubercle receives the name, among the English, of "mother yaw"; and the French patois of some West Indian islands is called a "maman yaw." While all the smaller yaws may entirely disappear this large one may remain, and, if neglected, ulcerate, eating its way into the tissues, causing extensive and often irreparable destruction of the soft parts, and setting up extreme constitutional irritation and emaciation.

The simplest and most ordinary tubercles of frambœsia do not usually ulcerate; but, attaining a certain size, form a yellow scab, shrink, and finally, on the crust falling off, leave purplish blue spots. In some instances the scabs form to such an extent as to produce crusts closely

resembling rupia ; if the scab be removed the surface left is commonly bright red in colour, and not at all unlike a raspberry ; but in old and asthenic cases the secreting surface is a dull yellowish white. When the yaws are in moist situations, as round the mouth, nostrils, or anus, on the perineum, or in the folds of the thighs and nates, crusts do not form : the lesion then closely resembles a syphilitic mucous tubercle. Unless on some very exposed part, or when ulcerated, the tumours are not very sensitive : they often itch and emit a curious musty and offensive smell. The yaw tubercles are relatively rare on the scalp and trunk, but are most frequent on the face at the corners of the mouth and nostrils, on the neck, arms, axillæ, legs, thighs, buttocks, and vulva.

The constitutional disturbance during this eruptive stage is variable : frequently the patient has a good appetite, is able to move about, and, except for the presence of the yaws, is apparently in good health : in other cases there are distinct fever, muscular pains, occasionally cramps, loss of appetite, debility, and anæmia. The eruption may last from a couple of months to a couple of years, successive crops of tubercles coming out at intervals ; but the duration largely depends upon treatment, food, and hygienic conditions. Occasionally one or two tubercles may appear some length of time after every symptom of the disease has disappeared. How far these are recrudescences of the original disease, or the effect of a reinfection, is at present uncertain ; probably the latter is the case.

The most characteristic features of yaws are that, unless pressed firmly, they are not tender ; and they do not degenerate and ulcerate except under irritation, bad treatment, and enfeebled general health. Their general tendency is to cure, gradually shrivelling up and falling off, and leaving a pigmented spot which eventually disappears. The lymphatic enlargement, which in some cases may be extreme, invariably subsides as involution begins. With the disappearance of the eruption the general health recovers ; and in ordinary cases no after-effects are experienced. All cases, however, do not terminate in this favourable manner ; this is particularly true if the patient be unable to get good food, be scrofulous and debilitated, or be placed in unfavourable conditions. In these cases, instead of the tubercles gradually disappearing, they ulcerate freely, involve deep parts, and, if death do not in the meantime occur from exhaustion, pyæmia, or septicæmia, they heal slowly, leaving irregular and extensive cicatrices. It is not uncommon in the West Indies to see men and women helpless cripples, as the result of contractions and stiffened joints following the healing of these ulcers. In the more severe cases gangrene of the toes and feet has been known to follow ; while in rarer instances ulceration of the nasal bones has been seen. These severe cases were much more prevalent in the past than now, and were probably due to imperfect methods of treatment—more especially to the abuse of mercury. Except in these extreme circumstances, the internal organs are unaffected ; few cases are fatal if properly treated.

**Diagnosis.**—The presence of initial papules, which enlarge to tubercles over which the epidermis splits, leaving bare a raspberry-like tumour which remains stationary for months, with a yellowish discharge, not painful, and tending to spontaneous cure without scarring unless ulcerated from irritation or defective health, should afford sufficiently characteristic features to distinguish frambœsia or yaws from other diseases. The principal affection with which it may be confounded is syphilis. From almost the earliest times in which we have any written account of yaws until the present day, the disease has been confounded with syphilis. Most of the older authorities describe it as the venereal disease; and a few medical men of the present time still believe in its syphilitic nature: but the majority of those observers who have had opportunities of observing both diseases are of opinion that frambœsia is a peculiar disease. The identity of syphilis and yaws has been supported by Mr. Hutchinson, in his preface to Dr. Numa Rat's essay on the disease, in which it must be admitted the accounts given of so-called yaws are indistinguishable from syphilis, and largely support Mr. Hutchinson's opinion that if "yaws be not syphilis, it is clear that it offers a very exact parallel to it." If yaws really presents the train of symptoms described in some of the cases quoted by Dr. Numa Rat, and upon which Mr. Hutchinson's opinions have been based, the disease is undoubtedly syphilis.

The present position of the controversy upon the specific nature of frambœsia is mainly one of diagnosis. There can be little doubt that in many cases described as yaws the diagnosis has not been too critical. All observers recognise, if they do not actually subscribe to the view, that the relationship of yaws to syphilis is a most intimate one. In my experience the similarity of the later manifestations of both diseases is remarkable. Moreover, the favourable effect of anti-syphilitic treatment in advanced cases of yaws points strongly to the syphilitic origin of the affection. There is further evidence in support of this view that in many places, notably Fiji, the incidence of yaws is coincident with an immunity to syphilis; while the recent observations made by Dr. Castellani upon cases of parangi in Ceylon, wherein he has demonstrated the existence of spirochætæ in the yaws tissues and juices, point strongly to a common origin for the two diseases. Certainly, the spirochætæ found in these cases of yaws appear to be identical with the *S. pallida* of Schaudinn, and now recognised generally to be a constant concomitant of primary and secondary syphilitic lesions (*vide* p. 46).

On the other hand, there are undoubted differences between syphilis and yaws which are difficult to explain: these are the mode of infection, the character of the secondary or later eruptions, the rare occurrence of tertiary frambœsial affections of the nervous system, the affection of the permanent teeth, etc.; but in most cases, on careful consideration, these differences are very often explicable. If syphilis and yaws are not precisely identical at the present time, yet there is much evidence to suggest that at one time they must have been most intimately related, and that

such intimacy was so great that the two diseases have developed from a parent form common to both. The last word has yet to be said on this controversy, and it seems advisable to withhold the formation of any very definite opinion until we are in possession of more exact scientific data as to the etiology of yaws.

**Treatment.**—Recognising that framboesia is a highly contagious disease, the first duty is to secure adequate isolation of the sick person. In Dominica, Grenada, and St. Lucia this first principle of prophylaxis is so well realised that infected persons are compelled to go into a yaw hospital under penalty of imprisonment. Compulsory segregation of the infected sick by themselves is, however, insufficient; no system of dealing with the disease can be considered efficient that does not further provide for (a) the isolation, as far as possible, of infected houses; (b) the thorough disinfection afterwards of these houses, and the destruction or disinfection of the clothes and bedding used by the sick; (c) the demolition of the wretched hovels, so common in endemic centres of this affection, which, by reason of the clinging of contagion to them, are so constant a danger to the public health; (d) a rigid enforcement of ordinary sanitary precautions; (e) the compulsory notification of all cases of yaws to the local sanitary authority.

The first essential in the actual treatment of the attack is the cleansing of the patient by means of warm baths and soap. Special care must be taken to avoid chills, as exposure to cold often causes a disappearance of the eruption, accompanied by much constitutional disturbance. The food must be nourishing, consisting of fresh meat, fish, rice, yams, and diluent drinks, combined with medicinal tonics. Locally, disinfectant lotions of boric or carbolic acids, or of corrosive sublimate, are of the first importance. The acid reaction of the secretion from yaws tubercles has suggested the use of alkali as a local dressing. Both Modder and Rat state that excellent results follow the use of lotions containing either bicarbonate of soda or carbonate of ammonia, of the strength of ten grains to the ounce. Sulphate of copper is efficacious as a topical application; so likewise are iodoform and weak nitrate of mercury ointment. The use of mercury in this disease needs the utmost care and supervision, as its abuse has been largely responsible in the past for the severity and fatality of many cases: it cannot be regarded as a specific remedy for the disease, as it is for syphilis, but, given in minute doses for a short time, mercury seems to act as a beneficial alterative. Of other internal remedies iodide of potassium with arsenic is very valuable, while in some cases iron and sulpho-carbolate of calcium are of the greatest benefit. Arsenic is very successful in the cases in which the eruption is badly developed or scaling, as in the *pian dartre* variety. When the feet and hands are affected, prolonged soaking in hot water is often required in order to soften and remove the thick epidermis; the exposed yaws growth can then be successfully treated on the lines indicated above.

During convalescence iron and arsenic should both be administered

over long periods, while in all stages of the affection perfect cleanliness and the best hygienic conditions are needed, both for the sake of the sick and of those brought into contact with them.

R. H. FIRTH.

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## VERRUGA

By Lieut.-Col. R. H. FIRTH, R.A.M.C.

**Short Description.**—A chronic infectious febrile disease, prevalent in certain narrow steep-sided and confined valleys on the western slopes of the Andes, characterised by an irregular prolonged and often intermittent febrile condition, with anæmia, followed sooner or later by the appearance of red tubercles of variable size on the cutaneous surface of the body.

**History.**—On the west coast of South America the disease is known under the names of Peruvian Wart, Verruga Peruana, Verruca Andicola, and Fiebre de la Oroya. It appears to be peculiar to Peru, being endemic in certain Cis-Andean localities, more especially in Huarochiri and Yauyas y Canta, at an elevation of from 3000 to 8000 feet above the sea-level.

The disease seems to have attracted attention from the earliest times, having been known in the days of the Incas. It was referred to as early as 1543 by Augustin Zarate in his History of Peru, in which he mentions a tract of country which "is very hot and unhealthy, the inhabitants suffering particularly from very malignant pimples (verrugas) or furuncles with deep roots, more dangerous than small-pox and almost as much so as the carbuncles of plague." The affection is also mentioned by Cosme Bueno in his *Descripciones Geograficas*, and by Tschudi in his work on Peru, dated 1843. The first scientific description of the disease was given by Salazar in a graduation thesis delivered at Lima in 1858, entitled *Historia de la Verrugas*, in which he clearly demonstrated it to be an endemic disease due to a poisonous virus. Since then numerous accounts of cases have appeared, by Dounon, Fournier, Bourse, and Tupper, chiefly based upon the outbreak of the disease in 1870 and following years among those employed in constructing the railway from Lima to Chicla, on the road to Oroya. A disease apparently identical with verrugas was reported in 1883 by Dr. de Havilland Hall as being prevalent at Zaruma in Ecuador.

**Pathology.**—Sections of the tumours shew that they consist primarily of a delicate fibrous stroma, the meshes of which are filled with round cells, the whole being enclosed in a sort of fibrous capsule. The smaller growths appear to spring from the papillary layer of the skin; the larger ones arise from the subcutaneous tissues. All the tumours are extremely vascular, the larger ones presenting in their centre cavernous spaces filled with blood. In some severe cases these vascular and warty growths are found after death not only on the skin but upon the mucous linings of the stomach and bladder, or even on the upper surface of the liver. Both this latter organ and the spleen are generally also much enlarged: but



yond these lesions on the viscera and skin, there are no evidences of at pathological changes.

Isquierdo has described a bacterium which he found in the morbid wths in some profusion. From his account this micro-organism ears to be from  $7\ \mu$  to  $10\ \mu$  long, beaded, and somewhat larger than bacillus of tubercle. The capillaries are often distended or varicose, ng filled with microbes which are also occasionally met with in the sels of the adjacent and apparently healthy skin. Isquierdo's accounts these organisms are not very precise; nor does he appear to have made isfactory culture experiments to indicate their specific relation to this ease.

**Etiology.**—Imperfectly as the pathology of this affection is worked t, it is not surprising to find its etiology still shrouded in some ecurity. From a somewhat extensive knowledge of the countries on the stern coast of South America, I am disposed to believe that the tribution of this affection is by no means confined to either Peru or uador, but that it is endemic also in Bolivia and the northern parts of ile.

Age, sex, and race have no influence upon verruga. That the ease is inoculable was demonstrated by the fatal experiment of niel Carrion, a young student in Lima, who, in order to elucidate the ease, inoculated himself with the blood of one of the warty growths;

death may possibly however, have been due to septic infection. e disease cannot be regarded as contagious, as patients suffering m verruga, even when treated in general wards, do not communicate affection to others. A popular opinion prevails in Peru that one ck can confer immunity against subsequent attacks. It is extremely btful whether the facts justify this belief; certainly, so far as my erience goes they do not. I met with several cases, both at Surco Matucana in Peru, in persons who assured me that they had had disease some years before, and had in the meanwhile remained quite from all symptoms.

The disease is undoubtedly endemic in certain well-defined areas, and native belief is that the affection is contracted by drinking water n particular springs and streams. Prolonged residence in the endemic ricts is certainly not necessary to contract the disease; but, on the er hand, notwithstanding Dounon's statements to the contrary, a mere age through the country, without either eating or drinking on the ney, or being thrown in intimate contact with the inhabitants, is not icient to produce it. It is difficult to eliminate the water-supply as a sible etiological factor in a country where sanitary arrangements are, the best, very unsatisfactory; but a close inquiry into the circum- ces and occupations of a large number of verruga patients convinced that the disease occurs only in those brought into intimate contact h the soil, notably those engaged in work which necessitates the dling of mud or earth—such as mining, tunnelling, and agricultural loyments, particularly upon rice fields and tea or coffee plantations.

This point has hitherto been overlooked by previous observers, and remembering that large numbers of the inhabitants of these verrug districts are the subjects not only of filariasis, but of helminthiasis generally, it is not improbable that the true solution of the pathology and etiology of this affection will be found in the association of the disease with some form of parasitic worm, whose free stage is passed either in water or mud, most likely in mud. I would strongly urge that future investigations into the etiology of verruga should be directed on these lines—more especially to the determination of the presence or absence of some form of hæmatozoon either in the warty growths or in the tissues generally of the affected person.

That verruga has anything in common with malaria does not merit serious discussion; it is true the fever of verruga may occasionally be very like malarial fever in form, but this is simply because the majority of those suffering from verruga are also the subjects of chronic malaria; and the fever thus complicated may assume an intermittent or even a remittent type. Malaria is exceedingly common in the Andean valleys, but it is in a few of these valleys only that verruga is found.

**Symptoms.**—There are practically three stages in this disease. First, one of incubation, lasting from fourteen to forty days, without any definite symptoms; second, a period of invasion and fever, followed by a third stage of eruption and convalescence.

The onset of the disease is marked by malaise, languor, headache, fever, and considerable gastric disturbance. The fever is usually irregular, and in many cases indistinguishable from a malarial intermittent, having daily cold, hot, and sweating stages. In some cases the fever is remittent. A characteristic and early symptom is the presence of dysphagia with cramp-like pains in the muscles. These muscular pains are often excruciating at night, being associated not infrequently with inflammatory swellings of the joints. The periosteal and myalgic pains are agonising at times and comparable with nothing experienced in other diseases. Accompanying these symptoms there is often a progressive anæmia, with œdema of the extremities, marked debility, and some tenderness or enlargement of the spleen and liver.

After these symptoms have lasted from one to nine months or a year they gradually remit or vanish with the appearance of a characteristic eruption, which consists either of raised spots about the size of a pea which develop into cylindrical, conical, or hemispherical tumours, varying in size from a raspberry to that of a pigeon's egg; or of minute, hard, movable, subcutaneous tumours, which may either disappear or increase in size into dusky red, shining, and itchy tumours.

The first variety of lesions are very vascular, itch, and, if scratched, bleed freely; ultimately they crust over and heal. If uninjured the warty growths remain stationary for some time, darken, and slowly subside, leaving after desquamation a discoloured area, which eventually disappears but no scar whatever.

In the case of the subcutaneous tumours the skin over them often

res way, and the morbid growths appear as fungating, fleshy swellings of a grey or black colour exuding an offensive sanguineous discharge. The size of these warty growths may vary from that of a pea to that of an orange, being in shape sometimes pedunculated like a mushroom, or again sessile and hemispherical. Not infrequently abscesses may form before the subcutaneous tumours break through the skin; or, after rupture of the skin, ulceration may ensue, in this case they may become crusted and rupial in character. The essential feature of all these eruptions is their vascularity; the warts either bleed spontaneously or at the slightest provocation, draining the already anæmic and debilitated patient.

The eruption is usually most abundant on the face and extensor surfaces of the extremities, especially on the knees, elbows, and malleoli. The trunk is less usually attacked. The number of excrescences varies from one to several hundred of all sizes and shapes. These tumours may also form on the conjunctivæ, in the nostrils, on the tongue, the mucous membrane of the pharynx, glottis, alimentary canal, and internal viscera. In these situations they may give rise to symptoms not only anomalous, but grave; such as hæmorrhages, suffocation, dysphagia, and ascites.

The disease generally lasts two or three months, or even longer; but not infrequently it is fatal earlier from hæmorrhages. In cases which survive there is usually profound anæmia, dropsy, or affections of the nervous system. The mortality among the indigenous populations of endemic areas is about 10 per cent—in whites rather higher; and in epidemics may amount to as much as 40 per cent. Cold has an unfavourable effect upon the eruption, causing it to be imperfectly developed, with an aggravation of the constitutional symptoms; while a diminished barometric pressure favours hæmorrhage. Consequently verruga cases are better in warm places and at sea-level than in cold and elevated situations. This largely explains the greater fatality experienced in some outbreaks as compared with others, the mortality being apparently related and in proportion to the lowering of the atmospheric temperature and pressure. Apart from hæmorrhages, considerable danger exists among the very poor and indigent from septic absorption in connexion with their unhealthy and often very extensive sores.

**Treatment.**—The first essential in the successful treatment of this affection is to remove the patient from the endemic area, and to transfer him, if possible, to a warm region at or near the sea-level. There is no known specific for the disease. All that can be done is to maintain the strength of the patient on general principles by a suitable and generous diet, combined with attention to the cleanliness and asepsis of the skin. Proliferating warts should be removed and ulcers treated by ordinary methods. As hæmorrhages are the most dangerous complication in this disease, styptics and compresses should always be kept available for sudden emergencies. Many of the fatal cases among the coolies and others suffering from verruga in out-of-the-way valleys arise from imperfect methods and facilities for guarding against profuse loss of blood.

This point has hitherto been overlooked by previous observers, and remembering that large numbers of the inhabitants of these verruga districts are the subjects not only of filariasis, but of helminthiasis generally, it is not improbable that the true solution of the pathology and etiology of this affection will be found in the association of the disease with some form of parasitic worm, whose free stage is passed either in water or mud, most likely in mud. I would strongly urge that future investigations into the etiology of verruga should be directed on these lines—more especially to the determination of the presence or absence of some form of hæmatozoon either in the warty growths or in the tissues generally of the affected person.

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Transfusion or saline injections are by no means uncalled for. During the eruptive and convalescent stages both iron and arsenic, with other tonics, are naturally of the greatest value; but at best the treatment of this disease is empirical and unsatisfactory, and so must remain until its etiology and pathology are better understood.

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### ULCERATING GRANULOMA OF THE PUDENDA

By C. W. DANIELS, M.B.

A CHRONIC granulomatous growth affecting the subcutaneous tissues of the pudenda and neighbouring parts. It occurs in many tropical countries, but differs in appearance in different races.

It was probably first described in India by Colonels Macleod, Maitland and other writers, as "serpiginous ulceration of the genitals," and under the name of "groin ulceration" has been the subject of discussion in



British Guiana for many years. In the Negroid races the manifestations are the most pronounced, and the following description applies to the disease, as it occurs in these races, in British Guiana and West Africa. The differences in the appearances of the disease as described in India and the Pacific Islands will be referred to on p. 711.

**Geographical Distribution.**—The disease is much commoner in some tropical countries than in others: thus, in many of the West India Islands it does not occur at all, and it is either extremely rare or absent in the Malay Peninsula, in Central Africa, and in some other tropical countries. Outside the Tropics imported cases only have been met with.

**Etiology.**—*Sex.*—It occurs in both sexes, the distribution of the disease varying in accordance with the position of the external genitalia.

*Age.*—It has not been observed before puberty in either sex. It usually commences in early adult life, rarely in old age.

**Histology.**—The growth is composed of round cells arranged in masses in the upper layers and papillæ of the cutis, and extends laterally beyond the visible seat of the lesion. The cells are mainly round, with a single nucleus surrounded by a broad margin of protoplasm containing basophil granules. In the deeper parts there are elongated cells with spindle-shaped nuclei which resemble connective-tissue corpuscles, while towards the surface especially, where the epithelium is fissured, polymorphonuclear leucocytes are numerous. Degenerate cells are rare, and there is no evidence of caseation or of breaking down of any part of the growth, which is vascular. Changes occur in the epithelium covering the growth, and in the connective tissue in its neighbourhood. The epithelium is thickened and the interpapillary processes are much elongated. The regular columnar arrangement of the deeper layers of the epidermis is lost, while there is either no pigment, or it is irregularly deposited in the subcutaneous tissue and in the epithelium towards the edge of the growth. None of the strata in the epidermis are well defined and no proper corneous layer is formed, the cells in the various layers differing little from one another.

The connective-tissue changes consist of swelling and degeneration of both the white and yellow fibres, which ultimately become replaced by the new growth. Beneath the growth, especially in the older parts, new fibrous tissue is formed, which differs from normal connective tissue in that it is composed of straighter and much more closely interlaced bands. Small masses of the growth are sometimes included in the meshes of this cicatricial tissue. The abundant formation of this dense fibrous tissue constitutes such an essential feature of the cutaneous form of this granuloma that "sclerosing" would be a better term than "ulcerating"; especially as any ulceration that does occur appears to be accidental, whilst the formation of dense fibrous tissue and deep scarring is invariable.

**Pathogeny.**—No organisms were found except in the superficial layers of the growth, by the earlier observers. Dr. Wise has recently

reported the discovery in the depths of the growth of *Spirochætæ*. Two forms were found resembling *S. pallida* and *S. refringens*. Injections of emulsions of the growth do not set up tuberculosis in guinea-pigs, while the absence of caseation and of any association with other tuberculous lesions militate against the view that it is a tuberculous skin lesion.

The position on or near the genitalia in both sexes suggests a venereal origin, but it is not associated with any manifestations of syphilis, nor of other diseases regarded as venereal: moreover, it does not appear to be highly contagious, as it may occur in husband or wife alone.

The down-growth of the interpapillary processes and the occasional formation of cell-nests may give a superficial resemblance to squamous-celled carcinoma; but a careful microscopic examination, a consideration of the clinical history, and the absence of any secondary growths and of any evidence of malignancy render this interpretation quite untenable.

**Clinical Course.**—The disease commences as an elevated papule, which in the male usually appears on or near the penis, and in the female on the labia minora. This papule causes little or no irritation, but steadily increases in size at a rate varying greatly in different cases. It spreads superficially, involving skin or mucous surfaces, or both, and its advance is accompanied by the formation of new granulomas at the edge, so that the whole mass appears as a coarsely granular, raised growth with an irregular outline, and as a rule without any ulceration. In a hairy part the granulomas are unusually coarse, and the hairs drop out. The older and more central parts are smoother, depressed, and often converted into dense, white fibrous scar-tissue. Beneath the growth a hard fibrous mass can be felt, and the surrounding healthy skin is stretched and sometimes puckered from the contraction of this scar-tissue. From the surface of the growth there is often an abundant clear discharge, which may have an offensive odour.

In the great majority of cases in the male the growth is primarily on the penis; and when on the glans is often so exuberant that the part is much distorted, and covered with coarse masses of the growth which conceal the meatus. The growth may extend for a fraction of an inch but never far, up the urethra. The formation of fibrous tissue beneath the growth may lead to stricture of the meatus.

Commonly, growth takes place not only by direct extension, but by the appearance in the groin or at the base of the penis of discrete nodules, which are probably set up by contact with the penile growth or its discharges. The groin is the favourite site of the growth, which extends along the soft moist folds, or into the most hairy parts, and is usually limited to these areas. From the fold of the groin it spreads between the scrotum and thighs on one or both sides, and in older cases creeps on to the perineum and backwards around the anus, into which it sometimes extends.

In the female the earliest growth is probably on the labia minora, but it readily extends up the vagina for a considerable distance, though it never invades the cervix. It also spreads along the cutaneous surfaces.

so that the labia majora may be invaded. The perineum, even when the labia majora are not attacked, is affected early, and the growth then passes backwards, surrounds the anus, and extends up the rectum. Sometimes it also spreads forwards between the thighs, and then by direct continuity may invade one or both of the groin-folds.

The result of the disease in women is more serious than in men. When the mucous surfaces of the vagina and rectum are both invaded, although there is no manifest sloughing, the growths in the two passages appear to become continuous in the deeper fascia, and thus recto-vaginal fistulæ result. These fistulæ may be numerous and, since both surfaces are composed of the growth, are incurable. Ulceration, either on the cutaneous or mucous surfaces, appears to be accidental. Since the tissue, though vascular, is of low vitality, and the epithelium softened and usually sodden from the discharges, cracks, abrasions, and superficial ulcerations are common in the larger growths.

The lymphatic glands are not enlarged, nor does suppuration take place. There must, however, be some obstruction of the lymphatics, as a chronic œdema—spurious elephantiasis—of the vulva, penis, or scrotum is common, without any evidence of filarial elephantiasis.

*Variations.*—In a country where the disease is common, individual variations are also common. These variations depend on the rapidity of the rate of extension, the varying tendency to formation of scar-tissue, as well as on the exact part involved. Thus, growth and destruction are more rapid on mucous than on cutaneous surfaces.

When other races, such as the Indians, are affected in a country where most of the sufferers are Negroes, the disease presents a different aspect on the two nationalities, which may be due to differences in the texture of the skin. The variations observed are mainly that the growth in the Indians is less coarsely granular in appearance and has less tendency to spread extensively than in the Negroes. In Fiji the Melanesian immigrants suffer from a disease which, though it resembles the ordinary form, differs from it in that the growths are softer, and more prominent, and spread less by continuity and more by contact, so that multiple discrete growths are more common.

Since much remains to be done in the investigation of the granulomas in the tropics it is impossible at present to state with any degree of certainty that the various granulomas occurring on the pudenda are one and the same disease. A condition limited to the mucous membrane of the last part of the rectum, and not involving the skin, is fairly common, and is often mistaken for dysentery on the one hand, and for syphilitic disease of the rectum on the other. Whether this is another manifestation of the granuloma described here may be doubted.

*Prognosis.*—The disease may exist for many years, and apart from the results of local complications does not affect the general health. No secondary growths occur, except those due to auto-infection by contact. There is always some tendency to cicatrization, which is sometimes marked so that the cicatrices may be not only extensive but complete.

When the growth affects the hairy parts, such as in the pubic regions, it is not uncommon for extension to cease when the whole of this region is involved. In rare instances complete spontaneous cure is effected by the conversion of the entire growth into a fibrous cicatrix.

**Diagnosis.**—The disease may be confused with any of the chronic ulcerations attacking this part of the body. When confined to the glans penis the growth is frequently diagnosed as squamous-celled carcinoma, but in any case of doubt the removal and microscopic examination of a portion of the tissue will speedily settle this point.

**The treatment** is unsatisfactory. Complete excision including the subjacent dense fibrous tissue is the only certain method of cure, but yet leaves a wound much larger than the portion excised. When the affected area is so extensive that excision is out of the question, scraping with a sharp spoon, the application of the actual cautery or of destructive agents such as salicylic acid, chloride of zinc, may give good results.

Antisymphilitic remedies in ordinary doses are useless, but potassium iodide in large doses, twenty or thirty grains three times a day, appears to increase the natural tendency to cicatrization; and in cases in which this tendency is strong the entire growth may become converted into a scar, and a cure result.

Antiseptic and other applications will reduce the fetor and prevent ulceration. In cases of stricture of the meatus dilatation or internal urethrotomy is useless, as contraction occurs almost at once. Amputation of the glans penis, as far as it is implicated in the growth, is requisite.

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## ORIENTAL SORE

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**SYNONYMS.**—*Oriental boil*: *Furunculus orientalis*; *Tropical ulcer*: *Boil or sore*; *Lahore, Mooltan, Scinde, or Kandahar sores*: *Penjideh ulcer, or sore*; *Aurangzebe*: *Lupus endemicus*; *Caneotica*: *Clou d'Alger*; *Clou de Gafsa*; *Clou du Nil*; *Biskra bouton*; *Orient beule*; *Lib-*

*Bouton de Crête* ; *Puru* (Malay) ; *Nisham-al-Tamar* (Baghdad) ; *Pashsha churdj* (Tashkend).

**Definition.**—A chronic local contagious disease met with and frequently endemic in certain towns and districts of India, Central Asia, the Levant, Algeria, and Malay Peninsula, characterised by the production of small pustules which, after assuming the character of a boil, undergo slow ulceration, healing after some length of time with loss of substance, leaving a bluish white depressed scar.

**History.**—Although several oriental medical writers refer to peculiar sores as prevalent in the past in various districts of the East, still this infection had attracted little attention in Europe before the Indian Mutiny 1857-58, at which time the palace and city of Delhi were occupied by European and native troops. The military cantonment had previously been situated two miles outside the city walls, and the disease was scarcely known amongst the troops ; but occasionally cases were met with there, at Lahore also, and at Mooltan. After 1858 the distemper came prominently into notice, as the troops in garrison inside Delhi were attacked with such severity that from 40 to 70 per cent were admitted to hospital suffering from characteristic sores, besides many who were treated out of hospital for similar complaints. The disease was very generally described as tedious and troublesome, though rarely fatal. When severe, or situated near a joint, the sores rendered the man unfit for duty ; and when occurring on the face were disgusting and disfiguring. In 1865 the Government of India appointed a Commission to investigate the disease. Ten years later a fresh inquiry was conducted by Drs. Lewis and Cunningham on behalf of the Indian Government. Since then a considerable amount of independent literature has accumulated concerning the nature and cause not only of the sores most prevalent at Delhi, but also of those analogous sores known to occur in many localities in different parts of the East. The more recent experiences of the French in Algeria and Tunis, and of the Russians in Central Asia, have again focused scientific attention upon these sores ; and at present by a general consensus of opinion they are all regarded as of the same nature and more or less identical in origin. For this reason it is very convenient to employ some common generic designation, such as that of oriental sore, suggested by Milbury Fox. The local names under which these sores are known indicate the places of greatest prevalence ; but, speaking generally, they are most common in certain tropical and subtropical climates, from 23° to 5° N., and from 15° W. to 20° E.

**Etiology.**—No age, sex, nationality, or occupation modifies liability to attack in those who fall within the influence of this disease. In endemic localities children rarely escape. Some authors, particularly those whose experience has been in Persia, state that new arrivals are especially prone to attack ; this feature has not been very generally recognised by Anglo-Indians. The *period of incubation* is variable, but usually some weeks elapse between exposure to the disease and develop-

ment of the papules. As a rule new arrivals do not get it until they have resided some time in the district, but cases are on record of a few days being sufficient. In other instances the affection has not appeared until the individuals had left the locality. In some cases inoculated by Weber the incubation was as short as three days. The affection appears to be quite independent of the nature of the soil: but its peculiarly definite geographical limitations indicate the influence of tropical and subtropical climates.

As bearing upon the possibility of one attack of these sores being a protection against a second, Colvill, quoted by Carter, states that at one time it was the custom in Baghdad to inoculate children with these sores so as to ensure the disease in a situation where the resulting scar would not be disfiguring. On the other hand, Murray and Fleming found that the sores could be successfully inoculated upon persons shewing scars of a previous attack. Similar results are recorded by Boinet and Dupéret, who have definitely proved that it is inoculable both in men and animals, notwithstanding previous attacks. They have also demonstrated the possibility of auto-inoculation. The occurrence of personal contagion from these sores appears to be very rare; and there is no evidence of hereditary influence. More recently Heydenreich has proved the communicability of the disease by direct inoculation. According to him infection is without difficulty produced by rubbing the powdered crust or the blood and lymph from non-ulcerated papules on abraded surfaces. The seasonal prevalence of these sores is chiefly in the latter part of the summer and in the autumn, that is, in subtropical climates, in August, September, October, and November; and in the first part of the cold season in the tropics.

In attempting to determine more precisely the causes of these sores we find: -(i.) that the disease is limited to certain places: (ii.) that healthy as well as weakly people are attacked: (iii.) that the disease can be conveyed by inoculation. The first two propositions point strongly away from constitutional causes, and rather to some local conditions of soil, insanitation, or water which favour the multiplication of the morbid agent outside the human body; while the third suggests that this agent, whatever it may be, is an organism. The very general occurrence of these sores on those parts of the body which are exposed at once suggests that the inoculation or infection may be effected by insects such as mosquitoes or flies; or again by dust or some accidental application of the virus to an abraded surface. In explanation of the excessive prevalence of these sores on the faces of young children, Laveran has pointed out that this is in them the most exposed part, and that they are less quick to brush away any insect which may be biting them.

The sores are equally prevalent upon wet soil or dry, on rock or sand, in high situations or low. It is difficult to shew that the endemic areas of the disease are areas of overcrowding, of accumulated refuse and excreta, or even of faulty alimentation; or that these sores are but the expression of a depraved nutrition from climatic or other unhealthy



influences. The great diminution in the number of cases of this affection which has followed ameliorated sanitary conditions of towns and districts, where formerly it was very prevalent, lends some support to such an opinion. Yet in the experience of many observers, including my own, these cases occur in camps and cantonments in which there is neither overcrowding nor defective hygiene, and also in persons free from any cachectic condition of body produced by unhealthy climate or other factors.

Newly-ad observers have attributed the origin of the oriental sore to the domestic water-supply, though they have not been equally unanimous in indicating the injurious element. Some French writers have attached importance to an excess of chloride of sodium and of the earthy salts, others have laid stress upon the disposing influence of large quantities of sulphate of lime in the streams of endemic areas. Clandy and Fraser pointed out the excess of nitrates in the wells where Mooltan and Lahore sores prevailed, while Alcock was inclined to blame the presence of sulphuretted hydrogen, resulting from the decomposition of organic matter in the water. Lewis and Cunningham suggested that excessive hardness may be an index of the deleterious property of drinking waters which in various parts of India are associated with the prevalence of the sores. It is true that in Delhi and elsewhere, since the disease of the water from wells within the city, the disease among British troops has abated; but the existence of similar chemical defects in the drinking water of many other places where the disease is unknown make this opinion impossible. In Algeria and Central Asia various impurities in food and drink, and the blocking up of the sudoriparous glands with dust, have been respectively assigned as active causes of this affection. If we admit that the water-supply is the vehicle by which the agent gains access to our bodies, the question arises whether it is taken into the system by swallowing, or whether it passes into the skin through the gland ducts or by abraded surfaces when washing. Against the acceptance of the drinking water hypothesis is the fact that many places where exceptionally good drinking water is in use are endemic centres of the sores. As Hirsch has pointed out, if this hypothesis were true, it would be difficult to explain why these sores have certain points of election in the body, such as the face and exposed parts of the extremities, and occur very rarely on the trunk, or why persons who are only acquainted with the internal uses of water are continually affected with these sores. If the domestic water supply be concerned in the production of these sores and ulcers, it is, as suggested by Murray and others, by reason of its containing some specific or parasitic body which finds attachment to the skin when the water is used for washing, and either spontaneously penetrates the cuticle, or else obtains entrance by some solution of continuity, such as a scratch, cut, or abrasion. As the weight of evidence is in favour of its parasitic nature, it is to be regretted that more extended and close inquiries have not been made into the fauna and flora of the sources of water, particularly of wells, in districts where these sores are prevalent. In discussing this subject

with various medical officers of Indian experience, my attention was drawn to the more frequent association of these sores with the use of old and foul wells than with canal supplies. It has long been recognised that oriental sore is a disease of countries in which the camel is a prominent domestic animal, and it has been maintained by some that the disease may be contracted from the camel, possibly by means of a tick or some fly. It is probable that investigations in this direction may supply the missing links of the chain of evidence concerning the life-history of the micro-organism which appears to be associated with the causation of this disease. Impressed with the similarity between the Leishman body of kala azar and the corresponding germ of oriental sore, which are morphologically and specifically identical, Sir P. Manson has suggested that oriental sore may bear the same relation to kala azar that vaccinia does to small-pox, and that possibly the virulence of the kala azar germ has been lost during its passage through the camel just as the variola germ is deprived of its virulence by passage through the cow. Although conjectural, this seems to be a point worth working at, as should this hypothesis prove to be correct, we may have ready to hand, in oriental sore, a means of preventing the severer and constitutional disease known as kala azar.

**Pathology.**—The histology of these sores has been thoroughly worked out; and, if sections be made of the initial papule before ulceration, no difficulty is experienced in demonstrating that the whole thickness of the skin and subjacent tissue is infiltrated with lymphoid and epithelioid (mesoblastic) cells, accompanied by more or less complete disintegration of the normal tissue-elements thereby. In the centre of the papule the infiltration by young round cells is so complete that little can be seen of the original tissue-elements but a few degenerated remains of hair-follicles or sweat-glands. Towards the edges of the diseased area the new cells occur in isolated clusters or groups, chiefly round blood-vessels or lymphatics. The infiltration does not seem primarily to involve either the hair-follicles or the sebaceous glands. The individual cells of this infiltration vary from 7 to 9  $\mu$ ; their nuclei from 5 to 6  $\mu$ : the nuclei are large, generally single, but in parts multiple. The anatomical structure of the papule and surrounding skin indicates that oriental sore is of the type of a granuloma; in fact, the most elementary microscopical examination of the lesions shew that it is a reaction of the skin against some virus of low virulence, which has produced granulomatous changes in the corium beneath and around the ulcer. So chronic are the changes which are sometimes met with that a close resemblance to tuberculosis may be occasioned. It is important to bear this in mind because it has several times been suggested that certain of these lesions are tuberculous. Doubtless, syphilitic and tuberculous ulcers have from time to time been placed in this group, but that there is an entity to which the term oriental sore is applicable, which is due to some virus different from syphilis and independent of tubercle bacilli, seems certain.

All authorities are agreed on this general statement of the histological

changes met with in oriental sore: but with regard to the causation of this peculiar process, we find some divergence both of opinion and of facts.

The first precise inquiries in this direction were made by Fleming and Smith in 1868. The former found in the diseased tissues certain small, highly refractive cells, which he took to be the eggs of a parasite; these were subsequently demonstrated to be disintegrated hair follicles; later, Smith found in the pus from the sores cells of various sizes and forms which he thought were ova, or, at least, larvæ of a species of ditomum. Both these observations were obviously founded on error due to the imperfect means of investigation available at that time. In 1875, Vandyke Carter, in examining specimens of a "bouton" sent to him by Weber of Biskra, believed that he found in the dilated lymphatic vessels a filamentous mould, with mycelial threads and gonidia. In these observations Weber concurred, but further investigations by Laveran and Kelsch demonstrated that the presence of these bodies was entirely accidental or adventitious. In 1880, Bordier, a French naval surgeon, described very similar growths. Lewis and Cunningham, in their report upon Delhi sore, dated 1876, and Geber of Vienna in discussing Aleppo evil, infer the identity of these oriental sores with lupus, and were unable to find any histological features in them at all suggestive of their being peculiar diseases.

Various micro-organisms have been found in the lesions, and put forward as the cause, such as micrococci by Boinet and Duperet, also by Duckaux, Chantemesse, Heydenreich, and Gessard; while certain streptococci and staphylococci have been suggested by Le Dantec and Auché. Up to the present time no micro-organisms of this kind have been satisfactorily shewn to be the causal agent in the disease. Cunningham in 1885 published the results of his examination of a specimen of Delhi boil, and described refractive bodies larger than lymphocytes in the tissues of the papular stage of these sores. They appeared to be cells from 8 to 10  $\mu$  in size, enclosing certain round and deeply stained bodies of variable size and grouping. Cunningham was inclined to regard them as representing various stages of some monadine organism. From an examination in 1889, of various papules of the Lahore Mooltan, and Scinde sores, removed before ulceration, I was able to confirm the presence of the cellular bodies described by Cunningham, but was disposed rather to regard them as results of some degenerative process in the cells than as parasitic protozoa. Somewhat similar conclusions were drawn by Riehl as the result of his examination of a single case.

The researches of recent years, conducted with an improved technique, have yielded more definite results. For this we are mainly indebted to Wright of Boston who, examining smear preparations made from one of these sores and stained by a modification of Romanowsky's stain, was able to detect the presence of generally round, sharply defined bodies from 2 to 4  $\mu$  in diameter. A few of the bodies were oval or elongated in form. These bodies were found to be packed closely together in the cytoplasm of the larger tissue-cells, occupying most of the available space

between the nucleus and the cell-membrane. Many cells contained twenty or more of these bodies. In thick sections of these sores the presence of these bodies give to the large cells in which they are situated the appearance of containing numerous basic staining granules of about the size of ordinary pus cocci, each surrounded by a clear space. Wright regarded these bodies as sporozoa and, believing them to be the causal agents of the lesions, proposed the generic and specific name *Heliosoma tropicum* for the parasites (*vide* p. 55). These observations have been confirmed by Christophers, James, and others. Further, there can be here or no doubt that these sporozoan, parasitic bodies present in the tissues of oriental sores are identical with the protozoan originally described by Colonel Leishman as present in certain cases of splenomegaly. A critical study of Wright's paper and of the accompanying plates indicates that the bodies he described are the same cells seen by Cunningham, Riehl, and Fitch, and described by them some fifteen to twenty years ago. The accurate recognition of their nature is due to a more perfect technique, and they undoubtedly represent some of the supposed plasmodia in process of sporulation described and figured by these earlier observers. This newer and more perfect knowledge of the pathology of these sores supports the view that they are a local infection by the Leishman Donovan bodies, an infection in which the vascular endothelium is probably mainly implicated. As regards the cycle of development of the parasite we have as yet no precise knowledge, other than that it is probably a stage in the life history of some flagellate. Be this so or not, the general pathology of oriental sores and the relation of the *Heliosoma tropicum* or Leishman Donovan bodies to the tissues of the lesion make it certain that in this affection the newly discovered parasite is acting as the causal agent in a focal granuloma of the skin. (For description of the Leishman Donovan bodies see p. 76.)

**Symptoms.** Usually the earliest sign of one of these sores is the occurrence, without any constitutional disturbance, of a small inflamed, itching or even burning area on the skin of some exposed part. The skin rapidly becomes bumpy and swollen, while in the centre of the inflamed patch a small seed-like body can be felt in the substance of the skin. This hard papule rapidly becomes deep red or purplish in colour, has a smooth and shiny surface, and may vary in diameter from an eighth to half an inch. As the papule increases in size the epidermis covering it shews a tendency to desquamate, the desquamation beginning from five to eight days after the first appearance of the papule. The epidermic scales first shed are fine, glistening, and dry, but as the deeper parts become invaded, so the scales become thicker, darker and moistened by a serous oozing from the surface of the papule. This may be in such excess as to form a small crust. Gradually the papule softens and, if inspected closely, is found to be marked with dilated blood vessels and several yellowish spots. After a variable time either the scab becomes detached, or the thinned epidermis gives way, leaving a small perforation from which issues a larger or smaller amount of thin, purulent fluid. In some cases before the detachment of the crust this may so on-

crease in size and thickness by continual accretion from below as to simulate rupia. The ulceration proceeds rapidly by erosion of the edges, and by the formation of fresh similar papules around it which in course of time break down in the same way, resulting in the coalescence of a number of small sores into one large ulcer with thickened edges and a base of sloughing cellular tissue. The edges are often so much raised as to make the ulcer appear deeper than it really is. The size and shape of these ulcers vary very much; sometimes they may be only half an inch in diameter, in other cases they may be one or more inches across. Usually they are oval in shape, but often present an irregular sinuous outline. The margin is generally ragged, thickened, and surrounded by an inflammatory areola of variable extent. The floor of the ulcer may be smooth, but is commonly uneven, proliferating in one part and disintegrating in another; it discharges a thin offensive pus which, if allowed to dry, forms thick adherent crusts. In some cases the discharge appears so to cling to the surface of the sore as to form a thick, slough like, yellow pellicle; often yellowish particles, about  $\frac{1}{16}$  inch in size, can be seen with a lens distributed on or through the sore; these appear to be degenerated hair follicles or comedones from the sebaceous ducts. The skin in the neighbourhood of the ulcer is generally infiltrated, and marked by small papules and yellow spots, indicative of extension of the disease.

At times these ulcers are extremely painful, while at others pain is completely absent. Ranking and some other writers have noticed a marked tendency to periodicity in the accessions of pain. Although in some cases the adjacent glands may be enlarged, and the lymphatics defined and cordy, the sympathy of the lymphatic system is by no means a constant symptom, and, as Hickman pointed out, is probably determined by the exact locality of the sores and the amount of irritation to which they are exposed. The ulcerative stage may last for months, the indolent nature of the sore and its intractability to treatment being characteristic. It is, however, in its healing that the oriental sore presents one of its most peculiar features. This process is greatly retarded by the formation of a scaly scab which must be carefully removed each day. Gradually the secretion lessens, the granulations lose their raw appearance, and healing commences from the centre and extends outwards; its course, however, is very slow, the new tissue being very liable to repeat the diseased process—to ulcerate, and start the sore afresh. Cicatrization ultimately takes place, the scar being more or less puckered towards the centre, and pigmented of a uniform bluish brown colour. If the attack has been on the face or other part where the cellular tissue is loose, the resulting disfigurement may be severe. The pigmentation of the scars of these sores often remains for years, but is in no way comparable or liable to be confounded with syphilitic pigmentation. In Baghdad the scars from these sores are known as "date marks."

The number and locality of the sores vary. Some patients may have but one or two, others may have as many as twenty. When multiple, the individual sores are often not so large as when single, and are said by



some observers to be less intractable. The disease is most commonly seen on exposed parts, such as the hands, arms, feet, legs, neck, or face; in children the face is the usual situation. It is very liable to attack abraded surfaces, wounds, and scratches. Insect-bites are very often the starting-points for them. In my own experience the dorsal surfaces of the wrist and borders of the forearms are the points most frequently attacked. The noses of dogs have been observed by many persons to be the seat of these sores, which they apparently contract when drinking.

The appearance of this disease is not always uniform; it may stop at any phase, and it may assume a chronic character when in the papular or boil-like stage, gradually subsiding and disappearing. In other cases even after the formation of a crust, this may not fall off, but persist until cicatrisation is complete beneath it; or sometimes the ulcerative process may be so vigorous and invade fresh tissues so rapidly, as closely to resemble *lupus exedens*. Some sores may become extremely inflamed from friction of clothes or other irritation; occasionally complications arise from inoculation with the virus of erysipelas or of phagedæna; this is, however, rare. When the sores occur on the persons of the scrofulous or syphilitic their clinical features are frequently modified. Any disadvantage arising from starvation, overwork, malaria, or the syphilitic and scrofulous cachexies, will modify the type of the sore and accentuate its intractability; but such constitutional or hereditary conditions do not necessarily dispose to the disease. In extreme and most exceptional cases, in which the patient is weakened by constitutional disease, or the sores are multiple, the resulting discharges and irritation may be very depressing and be accompanied by hectic fever.

**Diagnosis.**—In districts where the disease is known to be endemic this should not be difficult; as the appearance upon the face or other exposed part of an isolated papule, developing into a nodule, and this exuding, crusting, and then disintegrating into an obstinate ulcer under the crust, constitutes a distinctive set of symptoms. In some cases it might be mistaken for a syphilitic gumma or rupia, but the failure of specific remedies and the general clinical conditions should indicate a differential diagnosis. Although it has been confounded with ecthyma and impetigo this mistake should not readily occur. When present in a severe form upon the face there may be more difficulty in distinguishing it from rodent ulcer, lupus, or epithelioma.

From yaws it can be readily distinguished by remembering that yaws is almost limited to the coloured or negro races, while oriental sore attacks all races alike. Yaws is preceded by some febrile symptoms: these are rare in the sore. In yaws the lesions are always multiple or numerous, coming in crops: the boil or sore is usually single, and if multiple not numerous. Although both attack the face, yet yaws prefers the flexor surfaces, such as the palms and soles; whereas the boil prefers the dorsal aspects of the hands and feet. In both affections the lesion is that of a papule succeeded by a nodule; but in yaws the epidermis splits off in a few days, and the whole eruption is developed in a few weeks: ~~as~~



the other hand, the nodule of oriental sore may remain unchanged for months. When the crust of the yaw papule is removed only a moist tumour is found which, except in the very cachectic or when irritated, never ulcerates; when the crust of the oriental sore is removed an ulcer is exposed. Yaws leaves no scar, but oriental sore necessarily does so.

Malignant pustule, or external anthrax, can be readily distinguished from oriental sore by its size and extent of swelling, by its tendency to spread, by the livid tint of the skin and the early formation within it of more than one aperture, by the character of the slough, by the severity of the pain, and the marked constitutional disturbance; to this may be added the discovery of the specific bacilli of anthrax.

**Treatment.** Some authorities have advocated what is called the abortive treatment of these sores when in the early or papular stage. This needs some care and much personal supervision to be successful, and is best carried out by the application of Paquelin's or the actual cautery. The use of carbolic and other acids is not to be recommended, nor is excision. When ulceration has become thoroughly established, the use of caustic potash, nitric acid, fuming acid nitrate of mercury, or carbolic acid is valuable, but inferior to the judicious use of a Volkmann's spoon. For the removal of crusts antiseptic poultices may be applied; but in all dressings the greatest cleanliness should be observed and all irritative treatment avoided. Once the diseased process has been checked and the ulcer has taken on healthy action, the ordinary treatment for simple ulcers is sufficient. As many of the sufferers from these sores become rapidly debilitated in general health, care should be taken to supplement local treatment by a generous diet including wine or beer. Any evidence of malaria, scurvy, or syphilis should be met by appropriate treatment. In cases occurring in India I have generally found it necessary to remove the patient from the endemic areas; preferably by change to the hills. It is perhaps needless to say that in places where the sores are prevalent it is of the first importance to avoid the use of water, which may be infected, either for washing or drinking, unless previously boiled.

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## CLIMATIC BUBO

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**Description.**—A disease of wide geographical range, but chiefly occurring in tropical and subtropical countries. It is characterised by the development of buboes of non-venereal origin in the inguinal region in the folds of either the oblique or vertical group, but mainly in the former. The appearance of the bubo or buboes is associated with a rise in temperature, occasionally with rigors during the second week of the illness, with marked weakness and depression of spirits. Suppuration is the rule, but in several recorded cases the bubo has resolved and subsided. Bacteriological examinations have usually given negative results. The disease is sometimes spoken of as “non-venereal buboes” and as “pestis minor,” but the latter name is not intended to signify that the disease is mild, abortive, or ambulatory form of true plague, but a specific element allied with the prevalence of plague. The disease, although the cause of disablement for a time, is not of a fatal nature.

**Geographical Distribution.**—Climatic buboes have been reported in various parts of the world—from Japan, China, the Caroline Islands, Singapore and the Straits Settlements, Sumatra, Bengal and Calcutta in India; from Uganda, Zanzibar, Northern Nigeria, Cape Colony, and Madagascar; from New Orleans and the West Indies; from various stations of the British Navy. The “bubo malaricus” of Hungary is in all probability the same disease.

**Association with Plague.**—In the outbreak of plague on the Volga in 1878-79 Dr. J. F. Payne stated that whilst at Astrakhan at the mouth of the river true plague prevailed and many deaths ensued, at a town some 150 miles higher up the river the community suffered from an epidemic of buboes unattended by any fatal cases. The history of this epidemic points to a disease resembling the climatic bubo type of disease. During 1893 I reported 43 cases of climatic bubo met with in Hong Kong amongst Europeans, and during the same period the medical practitioners in the Straits Settlements reported many cases of the same nature. In this connexion it is interesting to note that true plague appeared in Hong Kong in the early months of 1894, and whilst yet the outbreak of climatic buboes prevailed; but plague never occurred in the Straits Settlements in other than sporadic form. In 1895-96 Prof. W. J. Simpson found among the soldiers of the Shropshire Regiment, who had gone from Hong Kong, where plague prevailed, to Calcutta, several cases of bubo of a non-fatal character; in 1896 plague appeared in Bombay and spread to other parts of India, but did not reach Calcutta until 1898. The soldiers of this regiment suffered from “climatic

buboes" whilst in Hong Kong during the prevalence of a severe epidemic of true plague.

On the east coast of Africa many cases of climatic bubo have been reported both in the British and German navies, and it is interesting in this connexion to note the discovery of plague in the Hinterland of British and German East Africa by Koch. In Cape Colony, where plague has prevailed for some years, cases described as "climatic bubo" were reported at Kimberley in 1904, although true plague had not occurred in that town. Clayton's cases occurred in China whilst plague was prevalent; and I saw a case of climatic bubo in a medical man returned to England from plague duty in Mysore in India.

These observations all tend to associate climatic bubo with plague, although plague does not necessarily develop in consequence of the prevalence of climatic buboes.

The name "pestis minor" was given to this complaint by the writer before the name climatic bubo was applied to the disease, without any idea of indicating mild, ambulatory, or abortive cases of plague thereby. Pestis minor is regarded by the writer as synonymous with climatic bubo, and is intended to indicate a specific ailment anticipating, running synchronously with, and continuing after outbreaks of true plague, but still preserving its own specific character. The association may be epidemiological merely, for a further etiological or pathological alliance has not been determined; but there are no accounts in literature of the prevalence of climatic bubo (pestis minor) where the possibility of contamination by true plague did not exist, although wide distances may apparently separate the actual prevalence of the two diseases.

*The Bacteriology of Climatic Bubo.*—In 1893-94 I found streptococci and staphylococci in the pus drawn from buboes of non-venereal origin, and occasionally a diplococcus. Prof. W. J. Simpson found a micro-organism resembling *Bacillus pestis* in the cases of bubo amongst some of the soldiers of the Shropshire regiment that had journeyed to Calcutta from Hong Kong where plague prevailed. In the case of a medical man suffering from non-venereal inguinal bubo, who came to England from a plague-infected district of India, Prof. R. T. Hewlett found:—"(1) A micrococcus liquefying gelatin, and white in growth, probably *S. pyogenes albus*; (2) a micrococcus not liquefying gelatin, probably *S. cereus albus*; (3) a minute stumpy bacillus inclined to bi-polar staining and staining well by Gram's method—this excludes plague." Dr. W. W. Stoney of Kimberley states that, in cases of climatic bubo examined there, a negative result was obtained. Prof. D. D. Cunningham found bacilli in the blood of cases of "pestis minor" (climatic bubo?) in Calcutta; these bacilli were, however, non-infectious, and were not considered identical with true plague bacilli. The fact that Prof. Cunningham found the bacilli in the blood in pestis minor was considered at one time to distinguish pestis minor from true plague; this distinction is now known to be fallacious as bacilli have been proved to occur in the blood in the earlier stages of the true plague infection.

Fleet Surgeon Clayton, R.N., describes four cases of climatic bubo in seamen of the British Navy on the China station. In three of these there was some evidence of local skin affection, "dhobie itch" as a rule. In spite of these cutaneous affections, however, the conditions he describes were undoubtedly of the nature of climatic bubo, although possibly the glandular trouble may have been determined in the first instance by irritation of the skin in the area drained by the lymphatics which converge to the inguinal group of glands. He gives the results of the blood examinations. In the case uncomplicated by skin affections the result was as follows:—The patient was put on the sick-list July 5, at Wei-hai-wei. On July 11, the blood examination shewed: red cells, 4,340,000; white cells, 16,330. Differential count July 13, when pus was evacuated from the swelling (697 counted), neutrophils, 65; eosinophils, 5; lymphocytes, 21; intermediate, 1; large mononuclear, 9. It is worthy of note that in true plague marked leucocytosis and also marked diminution of eosinophils obtain—exactly the reverse of the conditions present in cases of climatic bubo reported by Clayton.

The above considerations and observations indicate how defective is our knowledge, not only of climatic bubo or pestis minor, but of many points in the pathology of plague itself. In spite of experience of plague in many countries our knowledge of the disease, beyond the actual clinical signs and symptoms and the demonstration of the presence of a specific bacillus, is scanty in the extreme. Thus, the nature of the relation of plague in animals to plague in man is unknown; the difference between the bacilli described by Kitasato and by Yersin in regard to their relations to stains is as yet unsettled; there is a want of information concerning the life and existence of the plague bacillus outside the bodies of men or animals; and the various involution-forms of the bacillus so frequently met with in cultivation experiments all seem to shew that the plague bacillus may possibly exist in a double form in man, now in a non-infective or perhaps abortive form causing pestis minor or climatic bubo, now in an infective form causing true plague.

**Clinical Appearance.**—The patient, frequently after a period of an indefinite feeling of being out of sorts, becomes aware of a fulness in one groin, with a sense of local discomfort. The swelling increases from day to day, until by the fourth or fifth day it may assume the size and shape of half an orange, but with an indefinite outline. The skin becomes discoloured, at first mottled, then purplish in hue, and finally of a dull red colour; and œdema, pain on pressure and on movement appear, so that the patient cannot stand quite erect, and by the end of the first week of the illness walks with a limp. The temperature during the first week is seldom above 100° F., and the usual signs and symptoms of illness—headaches, foul tongue, loss of appetite, and either constipation or diarrhœa set in. During the second week the patient feels too ill to be about, and either stays indoors or altogether in bed; the temperature, of a remittent character throughout, may reach 101° or 102° F.; the bubo attains the size and shape of a Bath bun, and the patient becomes weak and low.



spirited. Towards the end of the second or the beginning of the third week this swelling shews signs of "bogginess," there may be a rigor and night-sweats, and in a few days' time distinct points (two, three, or more) of fluctuation can be felt. If left to itself the skin will break down at two or three points, and a sanio-purulent discharge escapes, which in a day or two becomes serous or sero-purulent, and several fistulous openings are established. If these sinuses are left alone, which of course they never should be, the discharge will continue for weeks; but if the mass be cut into by laying the sinuses open, and the gland excised, the resulting wound as a rule heals rapidly, so that by the end of the fourth week the patient should be fit for work again. The gland, when exposed by incision, is found necrosed and separated from its surroundings everywhere except at one point; and the surface of the gland is studded all over with purulent collections. When cut into, the gland-tissue is soft, friable, greyish in places, dark purple in others, with patches of pus of various sizes freely distributed. Although more than a single gland may be infected, one is always in a more advanced stage of disintegration than the others. The neighbouring glands, one, two, several, or all the groin-glands, may be congested, inflamed, and some of them shew purulent disintegration.

*The Duration.*—From the first appearance of the bubo to the end of the illness, provided the gland or glands are removed, the period is usually four weeks; suppuration appearing late in the second or early in the third week. When suppuration occurs early, and the diseased glands are excised without delay, the patient may be quite well by the end of the third week.

Some cases recover without suppuration, but in 54 cases which I treated resolution occurred in one instance only. Other observers have recorded better results, with resolution in a considerable number of cases. It is very rare for the glands in both groins to become affected during the course of the illness; but one side may become diseased after the side originally attacked has recovered.

*Age and Sex.*—The patients that I have treated were all males between the ages of 22 and 45, and the greater number of them were seafaring men, either engineers or sailors. Europeans seem more liable to the disease than are other races, but natives are not likely to seek the advice of a European doctor in an illness of the kind.

*Diagnosis.*—In coming to a conclusion that the disease is of non-venereal origin, the presence of genital, perineal, or anal irritation must be inquired into, and the parts carefully examined. In a filarial country the possibility that the glandular enlargement is due to filariasis must be entertained. When, however, the groin-glands are enlarged from filarial infection they suddenly become markedly painful, and the condition is always accompanied by a high temperature, "filarial fever," pains in the back, and often by chyluria. True plague may be the cause of the enlarged groin-glands, but careful search will shew that the glands elsewhere in the body are affected. It is well to remember also that these glands may become tuberculous, or even infected by hydatids.



**Prognosis.**—Climatic bubo is not a fatal disease ; after a period of depression and weakness the patient usually recovers quickly and completely, provided the ordinary régime for similar conditions is followed.

**Treatment.**—During the first week of the illness attempts should be made to cut short the enlargement of the groin-glands. This is best accomplished by rest in bed, light diet, attention to the condition of the bowels, and by the application of pressure on the gland itself. After cleansing the skin, a conical pad of lint and cotton-wool in alternate layers, of ample depth, some 6 inches in all, is placed (with the apex of the cone on the skin) over the bubo. A figure-of-eight bandage is then applied with the crossings on the pad and the loops embracing the thigh and body. It is advisable to place the limb between sand-bags, or on a splint, in order to prevent flexion of the thigh, whereby the bandage would be relaxed. The treatment by pressure may or may not be supplemented by the application of unguentum hydrargyri ammoniatum or linimentum potassii iodidi cum sapone to the surface of the skin before applying the pad.

As a rule the gland or glands go on to suppuration. When the evidence of pus is undoubted, the gland should be exposed by an incision of ample length parallel to the groin. The necrosed gland or glands are then removed and the part scraped, but not too roughly, with a sharp spoon. All sinuses running downwards towards the pubes should be scraped and drained by a counter-opening, the wound being packed with gauze and treated according to ordinary surgical rules. When healing has commenced the patient should have an increased amount of nourishment, and an appropriate tonic medicine. Early incision, before signs of pus are apparent, does not hasten the cure ; it is well, in this as in some other surgical conditions, to wait until the abscess is "ripe." Should the gland be cut down upon before suppuration is fairly well advanced, it will be found that the peri-glandular tissues are infiltrated with pus, that the hæmorrhage from the wound is profuse, and that the gland or glands are firmly bound down to the subjacent tissues in the neighbourhood of Poupart's ligament. The gland, if attempts are made in this stage to remove it from the deeper tissues, breaks down, and has to be removed piecemeal. Early incision and removal of the gland often appear to cause an extension of the inflammation to surrounding tissues, and pus may travel upwards amongst the tissues of the abdominal wall, causing considerable constitutional disturbance ; extensive incisions are necessary to procure proper drainage. The discharge from the wound appears, when the gland is removed early in the illness, to have virulent powers of infection, and its toxæmic character is indicated by the development of high temperatures, sometimes reaching 104° F. or even 105° F., which continue for several days after free drainage is provided for.

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## AINHUM

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Revised by J. M. H. MACLEOD, M.D., M.R.C.P.

**SYNONYMS.**—*Guduram* of the Iljes, a tribe of African negroes, *Faddat* of Nossi be and Madagascar; *Quqila* of Brazil, *Sukha pakla* (i.e. dry suppurative) of India.

**Definition.**—Ainhum (from the Nagos word signifying *to saw*) is the name applied to an affection of the toes, particularly of the little toe, peculiar to the dark skinned races, and is characterised by the formation of a deep groove, as if from the action of a slowly tightened ligature, around the base of the toe; this groove, gradually deepening, ends in the loss of the part.

**Geographical Distribution.** This peculiar affection was first observed among the natives of the Gold Coast by Clarke, who described it in 1860 under the heading of "dry gangrene of the little toe." In 1867, Dr. Silva Lima encountered it in Brazil and applied the name "ainhum" to it. Since then many cases of the disease have been reported in dark-coloured races, and chiefly in negroes, but it has not yet been observed in a European. It is widely distributed over the African continent, and cases have been recorded from various districts on the West Coast, Madagascar and the Zambesi on the East (Ashley Emile); Algiers, Fez, Cairo, and the Sudan in the North, and the Transvaal in the South (Murr).

Certain negro races are more prone to it than others, notably the Kroomen on the West Coast. It occurs also in South America, and was at one time extremely prevalent in Brazil in various towns such as Bahia, Rio de Janeiro, Pernambuco, and Buenos Ayres. The number of Brazilian cases is now diminishing, probably as the result of the steady decrease in the number of negroes in Brazil. Occasional cases have been met with in British Guiana. It has been observed also in certain parts of North America such as North Carolina, Louisiana, and Virginia; a few sporadic cases have been recorded from the West Indies. It has been repeatedly seen in India among the Hindoos in Dacca, Calcutta, and Bombay (Moreira). Several doubtful cases have been reported from China (Maxwell), some of which were probably examples of mutilating leprosy, with which ainhum has from time to time been confused. Cases have also been published from the Antilles, Gilbert Islands, and the Pine Islands of New Caledonia.

**Etiology.**—Ainhum occurs much more frequently in males than in females. It has been seen in children even as young as six weeks (Guyot); but the vast majority of instances occur in adults. According to Da Silva Lima it is liable to run in families; he states that he knew certain negro families in which every male member had ainhum. Duhring also describes a case in a negro whose father and mother were both affected, and Dupouy relates an instance in which grandfather, father, and two children were all the subjects of this disease.

There has been much speculation concerning the causes of this curious disease. It has been attributed to self-mutilation, or to such causes as the wearing of metal rings on the toes; but neither of these suggestions is borne out by the facts. Again, ainhum has been regarded as a tropho-neurosis; the evidence for this is no less insufficient. Various writers have asserted also that ainhum is a variety of leprosy (Zambaco, Collas, and Corre), or is an evidence of a "leprous diathesis" occurring in persons who are not the subjects of active leprosy (Ashley-Emile). Most observers consider, however, that it has nothing to do with leprosy, although, like any other disease, it may occur in a leper. My own impression is that the process is started by irritation or ulceration at the angle of the digito-plantar fold; in this situation in the negro the epidermis is often very thick, dry, and even fissured. It is conceivable that a chronic irritation or ulceration with a contracting hyperplasia of the dermis may be set up and maintained in such circumstances by the lodgment of dirt in this part, or by injury of it; owing to the direction of the folds of the skin this must tend to a linear and circular direction. The deeper the rut the more likely is it to contain irritating matters, and thus the process is apt to become permanent. Another but purely speculative explanation is to the effect that this peculiar condition is a form of scleroderma.

**Pathology.**—On longitudinal section of the amputated toe the skin and deeper tissues at the site of the constriction will be found blended together into a dense fibrous ring, the superficial epithelium being much hypertrophied. In the distal portion the cutaneous structures are slightly

thickened; the adipose tissue is much increased in some instances, not so in others; the bones are partly absorbed, the trabeculæ being thinned and filled with an oily material; the joints may be ankylosed, and their cartilages fibrous. Round-cell infiltration of the corium and obliterative endarteritis have been observed. According to Unna, there is in this disease "a primary degeneration of the skin, a sort of ring-formed scleroderma, with callous formation of the epidermis, which by its seat at the base of a limb leads to a secondary total necrosis, due to stagnation, a process which has a close resemblance to the artificial snaring of tumours. In spite of numerous histological investigations the nature of the whole process is still unexplained, largely because it is not clear from the descriptions which changes are primary and which secondary."

**Symptoms.**—The groove, which is the characteristic feature of *ainhum*, always begins as a shallow transverse crack, or rut, at the inner angle of the digito-plantar fold. As it deepens, the ends of the rut slowly extend upwards and outwards until they meet on the dorsum, or outer surface of the toe. The process is usually a very slow one, and may take years to complete. The deepening of the groove is not effected directly by ulceration, but by some process of constriction going on in or about the dermis. After a time the toe becomes enlarged to two or three times the natural size, so that ultimately the rounded and bulbous distal portion presents the appearance of a small potato or cherry attached to the foot by a narrow and more or less limp pedicle. The skin of the strangled portion is not materially altered in appearance, although to the touch the tissues have a somewhat soft and lipomatous consistence. When in process of time, and in consequence of the pressure of the constricting band, the bone or ligaments included in the pedicle become absorbed and lose their rigidity, the toe becomes everted, so that the nail, which may have become more or less deformed, faces outwards, or outwards and downwards. The constriction usually corresponds with the first interphalangeal articulation; occasionally it passes through the shaft of the first phalanx. Gongora relates a case in which, after the casting off of the two distal phalanges, the process was repeated in the stump. The narrow limp pedicle now permits the swollen toe to double under the foot in walking, thereby often occasioning much pain and inconvenience; for this reason, and as the toe is incessantly injured by catching on various objects, the patient, if this be not effected spontaneously or by accident, severs the pedicle. The slight resulting wound usually heals readily; occasionally, however, a small ulcer, in which exposed bone may be detected, may remain open for a time.

In some instances a certain amount of ulceration may be present in the depths of the constricting groove, particularly at the inner angle of the plantar fold; it is probably induced by injury or dirt. Although at times the toe itself may become inflamed and even gangrenous, active inflammatory manifestations appear not to be a necessary part of the process. When ulcerated or inflamed there is generally a good deal of suffering in the part; feelings of constriction are also complained of

sometimes. One observer (Dupouy) states that in his cases the onset of the disease was preceded by pains in the loin so severe that the patients were unable to stand. Other writers do not confirm this observation.

Both little toes may be attacked simultaneously, or one after the other; it may be after a long interval (30 years, Duhring). The little toe is that most frequently affected (45 out of 50 cases); more rarely it is the fourth toe (5 out of 50 cases, Da Silva Lima). The disease has also been seen in the fourth and little toes of the same foot (Pereira, Guimares), and also in the second toe (Gongora). Guyot records a case of the same, or a similar disease, in a native of the Isle of Pines, in whom not only the toes but the fingers were attacked; and it is said that the leg itself has been the subject of a similar amputating linear constriction.

**Treatment.**—In the earlier stages it has been suggested that the progress of strangulation might be arrested by division of the constricting ring. When the affected toe becomes useless, and is the source of pain or inconvenience, it should be amputated.

PATRICK MANSON, 1899.

J. M. H. MACLEOD, 1906.

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P. M.

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#### GOUNDOU

By J. M. H. MACLEOD, M.D., M.R.C.P.

**SYNONYMS.**—*Groz-nez*; *Henpuyé* or “dog-nose” of the Gold Coast;  
*Anakhre* or “big-nose” of the French Ivory Coast.

**Definition.**—Goundou is a peculiar affection of the nose, which is endemic chiefly among the natives of West Africa, and is characterised by symmetrical swelling of the sides of the nose, resulting from an exostosis of the nasal process of the superior maxillary bone.

**History.** This remarkable condition was first described by Professor Alexander Macalister in a paper read before the Royal Irish Academy on December 11, 1882, upon the existence of "horned men" in Africa, and was then regarded rather from an ethnological than from a pathological point of view. In 1887 Lamprey next drew attention to it, and described three cases which came under his observation whilst he was serving on the Gold Coast. For a detailed account of the disease, however, we are indebted to the writings, in 1895, of Maclaud of the French Navy, who had the opportunity of studying a number of cases among the inhabitants of the French Ivory Coast. Since then contributions on the subject have appeared from different parts of the globe, all of which have exhibited a striking unanimity with regard to the principal signs and symptoms of this disease.

**Geographical Distribution.**—Goundou occurs chiefly among the natives of the West Coast of Africa, the majority of the cases having been reported from the Gold Coast and the French Ivory Coast. It is so prevalent in certain districts of the Ivory Coast that Maclaud has estimated that, on the lower banks of the river Comoé between 1 and 2 per cent of the natives are affected with it. Cases have been recorded also from Sierra Leone (Renner), Angola, Uganda, and Zanzibar (Friedrichsen). It is not, however, confined to the African continent, for cases have been observed in the West Indies (Strachan), the Malay Peninsula (Braddon), Sumatra (Graham), and China (Maxwell).

**Etiology.**—The bony nature of the tumour masses was recognised by Lamprey as early as 1877, and it is now generally conceded that they are the result of a chronic subperiostitis of the nasal process and of the orbital plate of the superior maxilla; but the cause of the periostitis is at present unknown.

It occurs chiefly in the natives of certain districts of West Africa, and so far has not been known to attack a European. Maclaud's recognition of the affection in a chimpanzee proves that animals are not immune from it. It is said to be more common in males than in females. Since the affection may be found in various countries far distant from each other, such considerations as the character of the soil or atmospheric conditions can have little bearing on its causation. High temperature, however, may be a factor in its etiology, as almost all the recorded cases have occurred in the tropics.

The earlier writers on the subject believed it to be a racial peculiarity of the natives of the West Coast of Africa, and the cases which were recorded from the West Indies were explained as examples of atavism, the negroes affected being regarded as coming from an African stock (Strachan). But its occurrence in the Malay Peninsula and China, as well as in many West African tribes, proves that the influence of race is not an important etiological factor. Maclaud is responsible for another hypothesis which has attracted considerable attention, namely, that the disease is caused by the presence under the periosteum of the larynx of certain flies which have penetrated the nasal process from the nose.



But, as Sir P. Manson has pointed out, it is difficult on this hypothesis to explain the symmetry of the lesions, and for various other reasons it has not been generally accepted. Another explanation, which has been strongly supported by Chalmers and recently by Nell, is that the affection has a causal relation to yaws or framboesia. Chalmers observed that in his cases the goundon developed either in patients suffering from yaws or in those who were recovering from it and had a nasal discharge. He believed that the poison of yaws was taken up from the nasal mucosa and passed by the small vessels through the foramina in the nasal process, and there set up the "osteoplastic periostitis." Nell, on the other hand, regarded the yaws as the disposing cause, and believed the virus to be probably similar to that of phagedænic ulceration. Since so many of the natives of the districts in which goundon is endemic either have yaws or have suffered from this disease, a more definite relation than the frequent coincidence of the two diseases must be established before this explanation can be accepted.

**Symptoms.**—The disease usually commences in childhood. It may, however, not come on till later, as may happen when an adult native migrates into a district where the affection is endemic. Congenital cases have been recorded by Chalmers and Nell, but this is not the common experience, and the majority of writers on the subject describe it as an acquired affection. The disease is generally ushered in by frontal headaches associated with a sero-sanguineous discharge from the nose. These symptoms persist for about six months and then gradually disappear. During this time hard pea-sized swellings have developed on each side of the nose just below the level of the inner canthus. These slowly increase in size in a downward and outward direction, and assume an oval shape. About the age of puberty they may have become the size of an almond, at the age of twenty they may be as large as half a pigeon's egg on each side of the nose, and at the age of thirty they may have reached the dimensions of a hen's egg (Scheube). In a man aged sixty years Maclaud observed a goundon tumour the size of an ostrich's egg. As a rule the lesions are symmetrical; but unilateral tumours have been recorded, and one tumour may develop before the other. The growth of the goundon is remarkably slow, in some cases being continuous, in others ceasing with adult life or at some intermediate period of its course.

The skin over the tumour is normal in colour, and freely movable on the subjacent tissue. There is no marked inflammation associated with the appearance of the lesions, and they never break down or ulcerate. On palpation they present a bony consistence, are fixed, and, except in the early stages, are not tender. Friedrichsen, however, has recorded a case in which the lesions were painful on palpation, even after they had existed for nine years; and Chalmers has noted that they may become painful in wet weather.

The tumours cause a bulging in of the walls of the nose and constrict the nasal cavity, but they do not encroach on the septum of the nose or

the nasal cartilage, nor do they prevent breathing through it. The sense of smell is not markedly impaired by them, but the nasal mucosa is swollen and sensitive, and a nasal voice may be produced. The oral cavity and the hard palate are not invaded, and the general health of the patient is not interfered with. The only definite disadvantage attached to goniodon, besides the disfigurement, is that when the swellings reach a certain size they so interfere with the unfortunate patient's vision that he is obliged to bend his head down in order to see over the top of them. They do not, as a rule, invade the orbital cavity or injure the eyeball, but if they become sufficiently large they may displace the eye and even destroy it by pressure (MacLeod). When cut into, the growths are found to consist mainly of soft cancellous bone with a thin covering of compact bone which was formed beneath the periosteum of the nasal process of the superior maxilla, and may also have invaded the infraorbital plate.

**Treatment.**—Various forms of treatment, short of extirpation, such as iodide of potassium internally, have been tried, but with no apparent benefit. The only satisfactory method of dealing with the tumour is excision. For this purpose an incision should be made in the longitudinal skin retracted, and the bony growth removed by bone forceps.

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## TROPICAL DISEASES OF THE SKIN

By J. M. H. MACLEOD, M.D., M.R.C.P.

**Introduction.**—Tropical dermatology is at present in its infancy and has not yet attracted the attention which it deserves. Though various tropical skin affections have been more or less minutely described, the

ject as a whole is still in a state of disorder almost amounting to chaos. This condition of things is due to several causes. First, because we are indebted for the description of a large number of the tropical dermatoses to observers abroad who are not experts in this branch of medicine, and were without the facilities for working out the disease on the spot; secondly, because the nomenclature of tropical skin diseases is confusing, since many of the names applied to them are native generic names or place-names, and have been used indiscriminately for various conditions which differ in their clinical characteristics, etiology, and pathology; and lastly, because until recently observers seem to have paid little attention to the skin diseases affecting the white man in the tropics as to those of the native. It is difficult also to obtain accurate statistics even for the well-known skin diseases of the tropics, since not being as a rule fatal, they are apt to be missed out in health returns, or if mentioned, simply included under the general heading of skin diseases.

The skin diseases of the tropics do not differ essentially from those of temperate latitudes, but their clinical characteristics and etiology are modified by climate, clothes, or rather want of clothes, habits, customs, and differences in the power of the skin in coloured races to react to irritants. In this volume the skin diseases peculiar to tropical and subtropical climates will be dealt with, but reference will also be made to certain skin affections prevalent in temperate latitudes, which become considerably altered when they occur in hot climates and on dark skins.

The following provisional classification of the skin diseases of the tropics is based on that adopted by Jeanselme:—

### I. *General Infective Granuloma involving the Skin*

- Leprosy (*vide* art. p. 648).
- Syphilis (p. 736).
- Tuberculosis (p. 738).
- Yaws or Framboesia (*vide* art. p. 695).
- Verruga (*vide* art. p. 704).

### II. *Local Affections of the Skin of Microbic Origin*

- Oriental Sore (*vide* art. p. 712).
- Tropical Phagedæna (p. 739).
- Veld Sore (p. 743).
- Ulcerating Granuloma of the Pudenda (*vide* art. p. 708).

### III. *Skin Affections of Mycotic Origin*

- Favus (p. 745).
- Ringworm—
  - a. *Tinea tonsurans* (p. 746).
  - b. „ *circinata* (p. 746).
  - c. „ *cruris* or Dhobie Itch (p. 746).
  - d. „ *imbricata* (p. 747).

Erythrasma (p. 749).  
 Pityriasis versicolor (p. 750).  
 Pinta or Carate (p. 750).  
 Piedra (p. 753).  
 Mycetoma (p. 754).

#### IV. *Skin Affections due to Animal Parasites*

Craw craw (p. 759).  
 Water itch (p. 760).  
 Sand flea or Jigger (p. 761).  
 Myiasis due to the larvæ of various flies (p. 762).  
 Ixodiasis due to ticks (p. 764).  
 Bites of leeches (*vide* p. 959).

#### V. *Skin Affections due to the Climate of the Tropics*

Erythema solare (p. 765).  
 Lichen tropicus or Prickly heat (*vide* art. Vol. VIII. p. 743, 1899).

#### VI. *Dystrophies*

Vitiligo (p. 766).  
 Cheloid and hypertrophic scars (p. 766).  
 Ainhum (*vide* art. p. 728).

*Note.*—Several of the skin affections so classified above will probably in the light of further knowledge require rearrangement.

### I. *General Infective Granulomas involving the Skin*

**Syphilis in the Tropics.**—Syphilis is almost world wide in its distribution, and only a few remote parts of the globe, such as Greenland, various inaccessible districts in Central Africa, and certain rarely visited islands of the South Seas still remain immune from it. It was unknown, however, among the aboriginal inhabitants of tropical countries, and has been carried there by the white man or the Asiatic. At the end of the eighteenth century syphilis was introduced into the South Sea Islands by the sailors who voyaged with Captain Cook, and it has always been the case that as civilisation has advanced and new countries have been opened up to commerce, intercourse with the white man has led to the introduction of the disease. It has frequently been asserted that certain races are less susceptible to the disease than others, and this is doubtless true, but it is more probably the result of a higher state of morality, greater cleanliness, and better sanitation, than of racial differences.

Syphilis in the tropics does not differ essentially from syphilis of temperate latitudes, though its clinical manifestations may be considerably modified. The subject has not yet attracted much attention, and the records and statistics are often untrustworthy, since in health

ports syphilis is frequently confused with other venereal diseases, or with yaws or with tuberculosis, or included with yaws under a generic title heading such as "parangi" in Ceylon. For the most recent contributions to this subject we are indebted to Jeanselme, who has described syphilis in the Indo-Chinese peninsula, and to Scheube, for a general review of the subject published in 1902.

*Geographical Distribution.*—Syphilis is common in most parts of Asia, being specially severe in Bokhara, certain districts in India, and in China, Korea, and Japan. It is very prevalent in the Straits Settlements (Siam) and Borneo. In North America it is specially rife among the Indian population, and in the south it has proved a veritable scourge in Mexico and Brazil. In Africa it varies considerably in virulence. In British East Africa, for example, it is comparatively rare in the interior, though common on the coast; and in tropical Africa the natives seem to possess a certain degree of immunity to it, and take it in a mild form.

In the Madagascar district, however, it occurs in an exceptionally severe and malignant type.

When the disease is transmitted to a previously unaffected district or when it is prone to occur in a malignant form, decimating the population, and recalling the epidemic type of the disease which prevailed in Europe in the fifteenth century.

Though not essentially different, syphilis in the tropics may present certain peculiarities which distinguish it from syphilis in temperate climates; and one of the most striking of these is the far greater frequency of the extra-genital chancre in the tropics. This is partly because the native wears little or no clothing, and the skin, especially of his legs, is exposed to abrasion from the spines of prickly plants, splinters of wood, and bites and stings of insects and the like, and through such breaches of the surface the syphilitic virus readily gains entrance. Various native customs also tend to result in extra-genital chancres: such, for example, as the passing round of the water-gourd from lip to lip, and the habit of the native "medicine-man" of sucking bleeding and ulcerating sores. Owing to the want of cleanliness of the native, and the great facility to secondary inoculations, the primary lesions are apt to be infected with virulent micro-organisms and to become fulminating sores, and not infrequently to assume phagedænic characters.

In his description of syphilis in Indo-China Jeanselme has pointed out that the period of secondary symptoms is only slightly apparent in the native. Roseolar rashes are not observed, papular eruptions are mild in character and difficult to detect, and mucous patches in the mouth are rare. The tertiary period, on the other hand, is as severe in its manifestations as the secondary is slight. Some weeks after the initial lesion an eruption of nodular crusted syphilides, situated usually on the lower extremities, generally makes its appearance. These lesions rapidly increase in size, and are apt to break down, producing deep ulcerations, or by the drying up of a profuse discharge to become covered with thick crusts forming coarse rupia.

In association with the cutaneous lesions the joints and bones become involved, the epiphyses become swollen, and severe osteoepic pains arise. Some months later, through the spreading of the infection, malignant serpiginous lesions are formed, and large areas of tissue are destroyed, which on healing result in severe contractions and disfiguring scars. The joints become more and more involved, and the smaller ones, such as those of the phalanges, are apt to become detached, and the hands and feet to be reduced to almost unrecognisable stumps. Although in its course the disease may assume these precocious and malignant characters, parasyphilitic affections, such as tabes and general paralysis, are, according to Jeanselme, unknown in Indo-China, and Schreber has made the same observation with regard to syphilis in Japan, Kashmir, Corea, and the coast of Malabar. Syphilis contracted by Europeans from native women frequently assumes precocious characters, such as those described above, a fact which further emphasises the necessity of the adoption of more stringent measures of prevention among troops serving in tropical countries and in India.

Congenital syphilis is also common in the tropics. Jeanselme has described it in the Far East, and has noted that it attacks chiefly the cutaneous and osseous systems, and is associated with a heavy mortality. The usual characteristics, such as depression of the bridge of the nose, malformations of the skull, and rhagades at the angles of the mouth, are generally present. The triad of Hutchinson is said to be rarely observed: "the ear remains normal, interstitial keratitis is exceptional, and the teeth are generally well formed." Nervous lesions are common, such as idiocy, imbecility, spastic paraplegia, and hydrocephalus.

The treatment of exotic syphilis is the same as that employed in Europe. In European residents in the tropics the mercury should be administered by subcutaneous injection, as it is prone to irritate the alimentary tract when given by the mouth, and, if rubbed into the skin, to aggravate prickly heat. (For detailed treatment *vide* Vol. II, Part I, p. 368, and Vol. VIII, 1899, p. 814.)

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**Tuberculosis Cutis.** The prevalence of the various skin manifestations of tuberculosis in the tropics is a subject on which as yet we have no trustworthy information. Tuberculosis has a universal distribution, prevailing in latitudes as far removed as those of Greenland and Brazil. In certain countries and districts, however, its occurrence is rare; for example in Egypt, the Straits Settlements, and the Malay Peninsula. It is extremely prevalent in China and Japan. It affects all races, but the negro seems to be particularly susceptible. In warm climates up to



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Straits Settlements, and the south littoral of China. Cases have been reported in the Malayan Archipelago, in Borneo and Sumatra and in Australasia in the Fiji and Solomon Islands and New Caledonia. In tropical America it is met with in Mexico, South America, and the West Indies.

*Etiology and Bacteriology.* The clinical characters and course of tropical phagedæna all point to the conclusion that it is the result of the inoculation of a specific microbe in a susceptible individual, but no definite pathogenetic virus has yet been discovered. Bacilli and micrococci have been found in considerable numbers both in the false membrane and the exudation, as might be expected, but none of them has been proved to be specific. In 1884 Le Dantec described a bacillus which he believed to be the cause. It was a straight, or sometimes bent, motionless bacillus, which measured from 7 to 10  $\mu$  in length, was not stained by Gram's method, did not grow on ordinary culture media, and inoculation experiments gave negative results. These observations were corroborated in the main by Boinet, Petit, and others. A closely allied bacillus was described recently by Matzenauer of Vienna in hospital gangrene. These observations, however, though interesting and suggestive, are, in the absence of successful inoculation experiments, inconclusive.

A hot moist climate would seem to be one of the most important factors in the etiology of this disease. It occurs chiefly in the rainy season, and is most prevalent in low-lying swampy districts, imperfectly drained fields, the alluvial beds of rivers, and on the marshy lands about the sea-coast; it is rare in the highlands of the interior and in towns. It has been suggested by various writers that the pathogenetic virus has its habitat in the mud and mouldy vegetation of the marshes. There is no racial immunity towards the disease, but it is much more common in natives than in Europeans, because the native is much more insatiable in his habits, and, from tramping about barefoot and barelegged in the mud, more liable to inoculation. An important disposing cause is a weak state of health, such as may be brought about by exhaustion, want of food, or wasting disease. It readily attacks native soldiers during an arduous campaign, slave convoys on the march, half-fed coolies, and pioneers opening up some marshy jungle land. Of the wasting diseases which dispose to it, such as scurvy, dysentery, ulcer, eczema, and malaria, by far the most important is the last named, and in nearly every district in which tropical phagedæna occurs malaria is endemic. So close is the association between phagedæna and malaria that the name of "malarial ulcer" or "fever sore" has been frequently given to it. Under the heading of "fever sore" various kinds of ulcers more trivial in nature than tropical phagedæna, have also been included. These so-called "malarial ulcers" are not due to the malaria alone, but are the result of the inoculation of a specific virus in an individual rendered susceptible by the malaria. When Europeans are affected with tropical phagedæna malaria is usually responsible, and it has been frequently noted that a sudden spread of the gangrenous process is liable

take place with each access of fever. Cross, in his description of malarial ulcers of British Central Africa, stated that Europeans are seldom attacked with these sores till they have been a couple of years in the country, by which time the debilitating effects of the malaria begin to manifest themselves.

*Symptoms.*—Tropical phagedæna may develop on apparently healthy skin, but it usually follows an abrasion of the surface from traumatism, bites and stings of insects, or other such cause. It may also be a complication of some pre-existent sore such as a granulating lesion of the leg or a syphilitic ulcer. It may be mild and chronic in type, or assume acute characters and result in a terrible gangrenous sore which may have a fatal termination. It most frequently occurs on the dorsum of the foot and the front of the leg of natives, as they are uncovered and the parts most liable to injury and inoculation. It is not, however, confined to the lower extremities, and has been frequently observed on the hands and arms of coolies, specially when working at the rice harvest, and occasionally it has been known to attack the face and even uncovered parts of the body.

Soon after the specific inoculation takes place the skin of the affected part becomes inflamed, painful, and raised. In the course of a few days a vesicle or bulla, filled with sero-sanguineous fluid, forms in the centre of the inflamed area. The vesicle soon breaks and an unhealthy ulcer results, the floor of which becomes covered by a pulpy, greyish false membrane bathed in a fetid exudation of a brownish colour, which has been likened to wine-dregs. The ulcer spreads more or less rapidly, and may reach the size of a five-shilling piece or larger, the edges become raised and undermined, and a dusky-red areola appears round it.

In a mild case its progress may be arrested at this stage by a process of self-limitation. In several weeks or months cicatrization takes place, but the resultant scar is too often unsatisfactory, and liable to break down again on the slightest injury. On the other hand, when the virus is unusually powerful, or the individual affected is in a low state of health from a concomitant disease or other cause, the ulcer may take on fulminating characters and rapidly spread, layer after layer of the soft parts being attacked by the gangrenous process. The slough then separates and the skin and muscles are laid bare and decomposed, blood-vessels and nerves are dissected out, joints are denuded, and disarticulation may occur, and even the periosteum may be affected and the bone exposed. Associated with the local changes general symptoms usually supervene, such as weakness, pain, sleeplessness, and febrile attacks. In such cases a fatal issue may result from exhaustion and various complications, such as septicæmia, pyæmia, hæmorrhage from an eroded vessel, or suppuration of an affected joint. Should recovery take place, permanent disfigurement may be caused by contractures, mutilations, and ankylosis.

In many of its clinical features tropical phagedæna bears a striking resemblance to hospital gangrene, and several observers believe that the conditions are identical. It has been definitely proved to be auto-inocul-

able, but there is some diversity of opinion with regard to its infectivity. At first it was not believed to be contagious, but the observations of Le Dantec, Blaise, Bonnet, and others shew that it may be so.

*Diagnosis*—Tropical phagedæna must be distinguished from the ulcerations of yaws, syphilis, leprosy, and tuberculosis, from the various local ulcers now grouped under the heading of oriental sore, and from simple chronic ulcers. The diagnostic and pathognomonic sign which distinguishes it from these lesions is the presence of the greyish adherent false membrane. As has already been stated, there is considerable diversity of opinion regarding its relation to hospital gangrene. Le Dantec and others assert that the two conditions are identical, basing their belief on the clinical similarity and the fact that closely allied bacilli have been isolated in both. Hirsch, while admitting that certain of the cases of tropical phagedæna are hospital gangrene, protests against the inclusion of them all in this category, and points out that in many of the cases there is a tendency to self limitation, which in hospital gangrene is unusual, and that the infective power is far less.

*Prophylaxis and Treatment.*—Tropical phagedæna is so serious and intractable an affection, and is capable of incapacitating such a large number of labourers, natives, and troops campaigning in a country where it is endemic, that every effort should be made to prevent its occurrence, and to stamp it out. For this purpose it is of the first importance to protect the legs and feet of the native soldier. It would often be difficult to induce him to wear boots even if they could be provided, but adequate protection may be obtained by means of sandals and puttees of some hard material. When cases occur they should be isolated if possible, and to avoid overcrowding in the hospitals infected persons might be treated under canvas, or in temporary huts which can be destroyed afterwards.

The general treatment of the affection consists in placing the patient under satisfactory hygienic conditions, providing him with good food and fresh vegetables, and correcting, as far as possible, any obvious defect in his general health. When the phagedæna is associated with malaria, quinine should be prescribed, when it occurs in a syphilitic subject, mercury and iodide of potassium are indicated. Tonics such as iron and strychnine may be employed on general principles. Sir P. Manson advocates opium in full doses, for the double purpose of reducing the phagedæna and relieving the pain. In the case of Europeans, should the affection not prove amenable to treatment, a change of climate and a return home may be followed by great benefit. The local treatment, even in mild cases, to be successful, must be energetic and thorough. It is necessary in the first instance to destroy the false membrane and the sloughing tissue. This may be done by scraping with a sharp spoon, a general anæsthetic being given if the lesion be extensive. After scraping, the floor of the ulcer should be swabbed with pure carbolic acid or irrigated with 1 in 1000 sublimate solution, and finally dusted over with an astringent antiseptic powder, such as equal parts of iodoform, boric acid, and tannic acid. An antiseptic dressing such as dilute nitrate of

mercury ointment spread on lint should then be applied under a bandage. When the foot or the leg is affected the limb should be kept elevated. The sore should be dressed twice daily at first, and any recurrence of the membrane promptly dealt with by the curette and carbolic acid. In mild cases Tschudnowsky has recommended the application of the following preparation: iodoI, grs. 4; glycerin,  $\text{m} \frac{v}{i}$ ; powdered gum arabic, grs. x; and absolute alcohol,  $\frac{3}{5} \text{ i}$ , which forms an occlusive dressing by solidifying on exposure to the air, and so enables the patient to go about in comfort while healing is taking place. Instead of dressing the sore after the scraping, Sir P. Manson prefers to leave it exposed, and to allow a weak, warm, antiseptic lotion to trickle on its surface from an improvised irrigator.

In place of the sharp spoon a thermo-cautery may be employed to destroy the false membrane. In this way an occlusive scab is produced, which separates in about a week, and leaves a clean granulating surface.

As a rule, the granulations gradually become cicatrised, but occasionally, when there has been extensive destruction of tissue, the process may be very slow. When this is the case, Le Dantec advocates the cutting down of the raised edges of the sore and the application of strips of diachylon plaster over it, to draw the edges together and to exert continuous pressure on the granulations. Occasionally "Thier-ch-grafting" has to be resorted to, or the raising and dissection of the edges, and the bringing of them together by sutures over the wound as suggested by Plehn. In severe cases in which the gangrene is excessive amputation may be necessary, in which event the incision must be made well beyond the diseased tissue.

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**Veld Sore of South Africa** is an intractable affection of the skin which came into prominence during the late South African War (1899-1902), and was the source of much discomfort and a large amount of invaliding among the British troops. It may be defined as a special type of superficial ulcer which is edged by a fringe of exfoliating

epidermis, surrounded by an inflammatory areola, and peculiarly resistant to treatment. It occurs usually on the extensor aspect of the upper extremity, somewhere between the elbow and the fingers, but it may be found elsewhere, for example on the legs and feet. It begins as a small blister or a group of vesicles, which break down and give rise to a superficial ulcer, the floor of which resembles that of a broken cantharides blister; the edges of the sore are not much raised, but consist of an irregular fringe of broken epidermis. The lesions vary considerably in size from that of a threepenny piece to a florin, and they are frequently multiple. As a rule, suppuration is not a marked feature, but it may occur from a secondary pyogenetic infection, in which case the sores are apt to be associated with more or less inflammation of the neighbouring lymphatic glands. In their course they are chronic and singularly intractable; though they may have the appearance of healing and a scab may have formed over the surface, if it be removed *saropus* will still be found oozing from the exposed surface. When it does heal, however, little or no cicatrix is left, and even the hairs may grow again on the affected area; but, on the other hand, if there have been much secondary infection and deep ulceration, a depressed scar is certain to supervene.

This affection is well known to the Boers, and has been variously named "Gift zeer" (poison sore) in the Transvaal, and "Brand zeer" (burn sore) in the Orange River Colony. According to Mr. Bishop Harman several of the Australians present in that campaign recognised it as identical with a local sore which is prevalent in the Barcoo River district in North Queensland, and known there as "Barcoo Rot." It differs from the local sore of Natal, the so-called "Natal sore," in being a superficial epidermal lesion, whereas Natal sore is a granulomatous ulcer and belongs to the same category as the various oriental sores.

*Etiology.*—There seems little doubt that the affection has a specific bacterial origin. Prof. Ogston obtained from the lesions a micrococcus arranged in pairs like a gonococcus, which he thought might be specific, but he had not the opportunity of cultivating it. For this organism he suggested the name of *Micrococcus campaneus*. Mr. Harman also found a diplococcus, which he was able to grow on artificial media, and by inoculating himself with the pure culture he succeeded in producing on his arm a lesion presenting the characteristics of veld sore. This micro-organism he believed to be different from *Staphylococcus pyogenus aureus*, and gave it the name of *Micrococcus vesicans*. These observations are of great interest, and leave little doubt that the specific microbe has been discovered; but whether this micro-organism is a new species and merits a new name, or is an attenuated form of a familiar staphylococcus, has yet to be decided. The micro-organism doubtless gains entrance through some previous abrasion of the skin, such as may be caused by injury or the bites of insects.

Most observers are at one in regarding a low state of health as an important predisposing factor. Messrs. Harman and Pridmore both



noted that during the war it was more common in the cavalry than in the infantry, partly because the cavalry, being further away from their commissariat, were not in such good condition, and partly because they were liable to slight injuries from handling their trappings and wagons. Others observed that it was more prevalent in battalions on the march, and men out on the veld, than in the towns or camps, and that it rarely attacked soldiers till they had been out for a sufficient time to become run down by hardship, fatigue, and short rations. The season of the year does not seem to have any obvious influence on the prevalence of the disease.

*Treatment.*—To be successful the treatment of veld sore must be thorough. It is necessary in the first place to clip away all the exfoliating epidermis at the margins of the sore, for the micro-organism can be found penetrating the layers of the epidermis in advance of the edge of the blister (Harman). The surface of the lesion should then be thoroughly irrigated with sublimate solution (1 in 1000) or a compress soaked in this lotion applied. Boro-iodoform powder or calomel should be dusted on, and an antiseptic dressing applied under pieces of adhesive strapping. The dressing should be repeated daily till the sore is healed.

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### III. Skin Affections of Mycotic Origin or Tropical Dermatomycoses

The dermatomycoses form an important group of skin affections in the tropics, and result from the presence and growth in the epidermis of some variety of hyphomyces. This group includes favus, the various types of ringworm, pityriasis versicolor, erythrasma, pinta, piedra, and mycetoma. The majority of these diseases prevail in temperate climates, but a few of them, such as pinta, the peculiar form of ringworm known as *tinea imbricata*, and mycetoma, are confined to tropical zones. The tropical dermatomycoses are distinguished from those of temperate regions by the characters that they spread more rapidly and are associated with more inflammation and irritation; as the hot moist weather favours the growth of the fungi. In winter their activity diminishes, and the lesions tend to become quiescent and to resemble those of cold countries, or even wholly to disappear.

**Favus** has a wide distribution over the globe, but it is specially prevalent in the Eastern countries of Europe, Asia Minor, Egypt, and the southern littoral of the Mediterranean. It is independent of race, but there seem to be certain climatic conditions, not yet fully understood, which favour the growth of the fungus (*Achorion Schonleinii*). The chief factor in its diffusion is want of cleanliness; another factor may be

the closer association of certain peoples with animals which are susceptible to it and readily transmit it to man.

**Ringworm** in some form or other has a universal distribution. According to Hirsch it is most prevalent in India, the Malayan Archipelago, Cochin China, Japan, China, Abyssinia, Egypt, the West Coast of Africa, the West Indies, and Peru.

Since Sabouraud established the plurality of the fungi of ringworm much careful research has been carried out on the subject, and it has been proved that each species of ringworm has its own sphere of influence and that an investigation on the subject of ringworm holds good only for the particular country in which the investigation was conducted. The ringworms of the different European countries have been more or less carefully worked out, but those of the tropics form a vast and, to a large extent, unexplored field. They may be considered under the headings of *Tinea tonsurans*, *T. circinata*, *T. cruris*, and *T. imbricata*.

(a) *Tinea tonsurans*, or ringworm of the scalp, has not been sufficiently studied in warm countries, though various observers have reported it to be common. Courmont has observed it in negroes in Senegal, and states that certain of the cases are caused by the *Microsporon Audouini*, but that the majority are due to large-spored trichophytons which differ from those found in Europe. Castellani has recently isolated a trichophyton from three Cingalese children suffering from ringworm of the scalp, and recognised it as the *Trichophyton megalosporon endothrix*. A few isolated observations such as these represent the present state of our knowledge of the subject.

(b) *Tinea circinata*, or ringworm of the glabrous skin, occurs in the tropics in several forms. It may present slightly raised scaly patches with well-defined borders, which persist as solid patches during the course of the disease. It is more usual, however, for the patches to clear up in the centre, so as to form rings which coalesce and produce irregular gyrate figures. In this country *T. circinata* may be caused with almost equal frequency by the *Microsporon Audouini* and the large-spored trichophytons: but in the tropics only trichophytons have been isolated in cases of ringworm of the glabrous skin, and these appeared to differ from those found in European countries. Castellani isolated from a case of *T. circinata* in a European woman in Ceylon a peculiar trichophyton, which produced a "large acuminate non-powdered culture" on maltose agar. Sabouraud and Jeanselme have found in a series of cases of *T. circinata* of the solid-patch type, from the Sudan, a trichophyton which formed an acuminate brownish culture (trichophyton à cultures noires).

(c) *Tinea cruris* or *dhobie itch* is an intractable form of ringworm of the glabrous skin which attacks moist intertriginous regions, such as the crutch, axillæ, and the parts beneath the breasts in stout women. It is known in European countries as *T. cruris*, but in India, where it is particularly rife, it has been named "dhobie itch."

The name of "dhobie itch" or "washerman's itch" is used by laymen

in the tropics to denote any pruriginous affection of the skin, from the mistaken belief that the infective agent was usually clothes which had been handled by an infected dhobie. Under the heading of "dhobie itch" Sir P. Manson has included also cases of erythrasma and "pemphigus contagiosus." It is better, however, to restrict the name "dhobie itch" to the definite or regional form of ringworm which we call *T. cruris*, and which was once named *eczema marginatum* (Hebra). This affection is prevalent in many warm countries, and specially so in India, Burma, and China. There are certain clinical characteristics which serve to distinguish it from ordinary *T. circinata*. It begins as roundish, slightly elevated papules, situated about the crutch or axilla, which, owing to the moisture of the parts, instead of being scaly, not unfrequently present a raw, sodden appearance. The lesions increase in size, and the border becomes defined and raised. Contiguous patches coalesce to form irregular patches enclosed by a broad festooned border, which may be covered by thick scales or may present a number of oozing papules on its surface. Occasionally the patches may clear up in the centre to form circinate lesions. The affection may be limited to the inner surface of the thigh, or it may attack the genitalia, and spreading up both in front and behind may invade the whole of the bathing-drawers area. It occurs less frequently in the axilla and beneath the breasts.

In the warmth and moisture of these regions the fungus grows rapidly, and sets up considerable irritation and inflammation, further aggravated by the friction of these parts. So sore may the lesions become that the patient may be compelled to remain in bed. The temptation to rub and scratch is irresistible, and the secondary inoculation with pyococci, followed by an impetigo or an abscess, is prone to occur. The irritation is naturally worse in the hot season, and when the patient is warm in bed.

It is probable that more than one variety of fungus of the trichophyton type may cause dhobie itch; moreover, certain of the cases may be of animal origin. From two cases in Ceylon Castellani isolated a trichophyton which grew on maltose agar in the form of greyish crateriform cultures. In some cases a variety of hyphomyces has been found which would not grow on artificial media. Cases of this nature have been described by Sabouraud from Japan, Tonkin, and Indo-China, and by Castellani in Ceylon.

(d) *Tinea imbricata* is the name given by Sir P. Manson to a peculiar type of tropical ringworm which is endemic, chiefly in the Malay Peninsula and the South Sea Islands, and attacks large numbers of the population. Various synonyms have been applied to it, of which the best known are Tokelau ringworm (from the Union or Tokelau Islands where it is rife), Pita, and Cascadoe. From the South Sea Islands it has gradually spread to the East Indies, China, and the Straits Settlements. It has recently been observed in Brazil (Paranhos). It is mainly confined to the Papuans and Malays, though it may attack other natives.

The clinical peculiarity of this type of ringworm is the imbricated

formation of its scales, which are arranged in concentric circles with the base of the scale towards the periphery, or in wavy parallel lines suggesting watered silk. Soon after the infection takes place a slightly raised brownish patch becomes visible. This tends to clear up in the centre by the loosening and breaking of the epidermis, but spreads peripherally. New central lesions continue to form till a concentric system results, made up of rings of scales which overlap in an imbricated fashion. By coalescing with other systems elaborate figures are produced and large areas of skin are invaded. Occasionally the nails are attacked, and become in consequence brittle, discoloured, opaque, and striated. According to Jeanselme the hairs are not involved though the scalp may be affected, but Sir P. Manson has observed cases in which the hair also was implicated. A peculiarity of this affection is that when the scales become detached a leucodermic area is left, which gives the patient a somewhat piebald appearance. The disease is associated with severe pruritus which leads to scratching and sequels, such as impetigo, eczema, and adenitis. Like other forms of tropical ringworm, it is at its worst in the hot season and is apt to become quiescent in winter.

*Tinea imbricata* is a highly contagious affection and has been successfully inoculated from man to man. It is due to a fungus situated in the epidermis and the scales in far greater abundance than the fungus of *T. circinata*, and it is to Sir P. Manson that we are indebted for the first description of it. It belongs to the group of the hyphomycetes, presenting mycelial filaments, which branch dichotomously, and round, oval, or quadrilateral spores arranged in rows or in irregular clusters, but the botanical species in which it should be included is still undecided. Tribondeau, who studied the subject in the natives of Polynesia, noted mycelial filaments terminating in club-shaped, sporulating fructifications of the type found in *aspergillus*. Jeanselme, although he found similar fructifications, was unable to verify the continuity between them and the mycelium described by Sir P. Manson; he believed that the fungus, though differing in certain details from the trichophytons of ringworm of animal origin, was closely allied to them. This observation is all the more reasonable in the light of our knowledge that *aspergillus* frequently grows in association with the ordinary ringworm fungi, and that it is very common to get a symbiosis of these fungi in cultures. The cultivation experiments have not, so far, been uniformly successful, and until they are the exact species of hyphomycetes which causes this form of ringworm must remain undetermined.

*The treatment of ringworm in the tropics* does not differ essentially from that of ringworm in temperate latitudes, except that, as a rule, it must be more energetic than in cold climates. For a description of the treatment of ringworm in general the reader is referred to Vol. VIII., 1899, p. 853, as the treatment of the special tropical forms only will be considered here.

*Tinea cruris* or *dhobie itch* is a most intractable affection, and necessitates extremely active measures. The affected regions should first be

scrubbed with hot water and soft soap on a piece of flannel, to remove the crusts, scales, and discharge. After that a strong antiparasitic lotion or ointment should be thoroughly rubbed in once or twice daily. For this purpose in mild cases ointments containing sulphur 10 per cent, salicylic acid 5 per cent, or pyrogallic acid 5 per cent may be employed; or the nascent sulphur treatment may be resorted to, which consists in the application of a 6 per cent solution of hyposulphite of soda on lint covered with oiled silk for about ten minutes, followed by painting with 3 per cent solution of tartaric acid. In severe cases the time honoured Velminck's solution of sulphuret of calcium may be employed (1 oz. quick lime, 2 oz. precipitated sulphur, 15 oz. water, boiled together in an earthenware vessel, then reduced to 10 oz., and the clear sherry-coloured fluid decanted after subsidence), and should be painted on every night for a week, this will generally be followed by recovery. In certain cases even these remedies prove ineffectual, and stronger measures must be adopted. It is in such cases that chrysarobin has been found to be of great value. It is best applied in the form of a 2 to 6 per cent ointment rubbed in twice daily till the skin around the affected patch reacts and becomes red and inflamed, the rubbing is then stopped, as the reaction generally indicates that a cure has been effected. It is necessary in employing chrysarobin to warn the patients that the drug stains the clothing, and that, as it is a powerful irritant, it must not be allowed to reach sensitive parts like the eyes. For at least a month after active treatment has apparently cured the lesions, the part should be painted over every second day with a 10 per cent solution of tincture of iodine in 60 per cent spirit to prevent any recrudescence of infection. As a prophylactic measure Sir P. Manson recommends that short cotton bathing-drawers should be worn, and changed daily; and that the skin of the crutch should be frequently powdered with a dusting powder containing equal parts of boric acid, zinc oxide, and starch.

*Tinea imbricata* requires similar treatment to *T. cruris*. It is unsafe, however, to place such an irritating remedy as chrysarobin in the hands of ordinary natives, and as a substitute Sir P. Manson recommends a linimentum iodi of double the strength of that of the British Pharmacopœia.

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**Erythrasma** is a mycotic affection of the skin which is widely distributed in the tropics as well as in temperate climates. It has frequently,

however, been confused with other dermatomycoses, and as Sir P. Manson has pointed out, certain of the cases which have been described under the heading of dhobie itch were cases of erythrasma due to the *Microsporum minutissimum*. The clinical features and treatment of the disease in warm countries require no special description (*vide* Vol. VIII., 1899, p. 865).

**Pityriasis versicolor** is also a common dermatomycosis in the tropics. When it attacks the native it usually produces yellowish ground-glass-like patches, which have been aptly compared to thin coats of yellow paint. The specific fungus (*Microsporon furfur*) has been readily isolated from the lesions, but cultivation experiments have not been more successful in the tropics than in Europe. In the natives of Ceylon, Castellani has described three varieties of *P. versicolor*; namely, two yellow types, to which he has given the name of *P. versicolor flava*, and a black type, which he has christened *P. versicolor nigra*. The first variety of *P. versicolor flava* usually attacks the face, neck, and the upper part of the trunk, and the affected patches are yellowish in tinge, and smooth; the second variety generally attacks the arms and legs, and the patches are whitish-yellow, and covered with fine scales. In pityriasis nigra the affected areas are black, slightly elevated, and scaly. Each of these types is believed to be caused by a variant of the *Microsporon furfur*, which can be distinguished microscopically.

The treatment of *P. versicolor* in the tropics is similar to that employed in Europe (*vide* Vol. VIII., 1899, p. 864).

The consideration of erythrasma and *P. versicolor* of the tropics, especially in the light of Castellani's recent observations, naturally leads us to the consideration of the group of epiphytic disease of the tropics, characterised by the presence of variously coloured patches, and generally described under the heading of "Pinta."

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**Pinta.**—Syn. *Mal del Pinto*, *Spotted Sickness*, *Peint*, *Caraté*, *Cute*, *Catí*, *Pannus Carateus* (Alibert).

**Definition.**—Under the heading of Pinta, Caraté, and various other names, a peculiar form of epiphytic skin disease of the tropics has been described, which is characterised by the appearance of spots and patches of different colours on the skin, and sometimes on the mucous membranes.

**Geographical Distribution.**—Pinta is endemic, chiefly in the tropical countries of the Western Hemisphere, such as Mexico, Central America, Venezuela, Chile, and Peru. Caraté is particularly rife in Columbia, affecting in some parts one out of ten of the population; and catí occurs in Guatemala and Honduras. In Africa a similar affection has been described in Tripoli (Legrain), in Egypt (Sandwith), and on the Gold Coast (Browne). Whether these variously designated affections are



tical is at present uncertain, but they are at least so closely allied as to suggest that they are caused by variants of the same species of fungus.

*Etiology.*—One of the most important disposing causes of this peculiar dermatomycosis is a hot, moist climate. In the countries where it is endemic it is found mainly in low-lying marshy lands about the banks of rivers. It prevails chiefly in the hot rainy season. Want of cleanliness, poor clothing, bad hygienic conditions, and insufficient food are all disposing factors. It attacks the poor rather than the rich and well-fed. It rarely affects the white population, but, in a district in which it is endemic, is rife among the negroes, Indians, and half-castes. In British Guianas, for example, the Europeans escape almost entirely, while about 50 per cent of the Caribs are attacked (Cran). Age and sex have nothing to do with the etiology. The disease is transmitted from man to man, but it is believed in Mexico that mosquitoes may convey it.

The cause of the affection is some form of chromogenetic fungus in the epidermis; the differences in colour are due to differences in the pigment formed by the fungus. Another factor in the colour of the lesions is the precise situation of the fungus in the epidermis; for when the lesions are black or blue the fungus is found to be situated superficially, but when they are red or grey to be deeper in the epidermis. But whether different species of fungi are responsible for the various forms of this condition, or whether under certain conditions the same fungus may produce different pigments, are at present unsolved problems; so that in the present state of our knowledge it is well to keep an open mind on this subject.

In 1881 Gastambide described a hyphomyces in the scales of pinta, which presented an agglomeration of ovoid or roundish spores 6-8  $\mu$  in breadth and 10-12  $\mu$  in length lying between the epidermal cells. Each spore possessed a transparent membrane containing a large number of darkish granules suspended in a yellow fluid. Small fragments of mycelial threads were also observed, which shewed no tendency to branch dichotomously. Montoya, in 1898, in a thesis on caraté in Columbia, isolated from the scales a number of fungi which belonged to the *Aspergillus* species. These presented long slender mycelial filaments which branched dichotomously, and gave off here and there short branches terminating in large fructifications like those of *Aspergillus*. When grown on artificial media, coloured cultures were produced corresponding to the colour of the scale from which the fungus was isolated. He also observed fungi of the species of *Monilia* and *Penicillium*, but failed to detect a hyphomyces like that described by Gastambide.

Darier has recently published a case of caraté, or an allied dermatosis of South American origin, in a white man, which began as red patches, and gradually invaded the whole of the skin, except the face, temples, and ears. From the scales he isolated a hyphomyces, which Bodin succeeded in cultivating, and believed to be a trichophyton.

*Symptoms.*—The eruption generally appears first on the uncovered

parts of the body, and may attack the face, neck, forearms, wrists, legs, and ankles. It is preceded by more or less itching. But no definite constitutional symptoms are associated with its presence. It begins as one or more small discoloured, scaly spots, which enlarge and coalesce to form irregular patches. New lesions follow by auto-contagion, and gradually increase in size till the whole of the glabrous skin, with the exception of that of the palms and soles, may be involved in a patchy fashion, which gives to the patient a grotesque piebald appearance. The colour of the patches varies; it may be blue, violet, black, red, grey, yellow, and white, the red variety occurring only in white skins. The tint of an individual patch remains constant till it begins to recede, but in certain cases patches of different colours are present in the same individual. The affected skin becomes dry and coarse, and emits an offensive odour, which has been compared to that of a mangy dog or of dirty linen; this odour is not, however, specific, but is the result of perspiration and lack of cleanliness. More or less itching is associated with it, which is specially vexatious at night, and apt to lead to excoriations from scratching, and secondary lesions produced by pyogenic inoculation.

Two stages in the course of the affection are described by Jeanselme, namely, an active stage of pigment-formation ("stage of hyperchromia") and a late atrophic stage characterised by the disappearance of pigment ("stage of achromia" or pseudo-vitiligo). If the patient be insufficiently treated, the stage of hyperchromia may persist for many years. When the stage of achromia begins, the pigmented patches desquamate and disappear, leaving white patches in their place; this process begins at the centre of the patch and spreads towards the periphery. The loss of pigmentation is caused by the action of the parasite on the melanin of the skin, and is noticed first over bony prominences subject to rubbing, such as the elbows. Though the palms and soles are not seats of the pigmented patches they are occasionally subject to much thickening of the horny layer, and the consequent formation of deep cracks, which readily bleed. Neither the nails nor the hairs are attacked; but if the scalp be affected the hairs tend to become atrophic, lustreless, and may fall out. According to Barbe, in long-standing cases the mucous membranes of the mouth, prepuce, and vagina may be coloured. The eruption, though not associated with any serious constitutional symptoms, may yet be a source of annoyance to the patient on account of the itching which is generally present, and is best marked when the scalliness is excessive. The affection is progressive in its course unless it is thoroughly treated, the black variety spreading more rapidly than the red or the white.

*Diagnosis.*—The skin affections with which pinta is most liable to be confounded are vitiligo and chloasma. Extensive cases of vitiligo, indeed, have from time to time been described under the heading of pinta or caraté. Vitiligo, however, differs from pinta in being more symmetrically distributed, in being neither scaly nor itchy, and in the fact that no fungus can be isolated from it. Chloasma is disposed also

to be distributed symmetrically, and is not scaly. Occasionally cases of pinta have been mistaken for leprosy, but apart from other differences the patches in pinta are not anæsthetic like those of the more serious disease.

*Treatment.*—The treatment of this affection is the same as that for pityriasis versicolor, and consists of scrubbing with soft soap and the application of antiparasitic ointments containing sulphur or chrysarobin, or lotions of hyposulphite of soda, or of tincture of iodine. In pinta, as in all the dermatomycoses, the clothing worn while the disease was active must be destroyed or disinfected.

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**Piedra.**—Syn.: *Trichomycosis nodosa* (Juhel-Rénoy). Piedra is the name given to a rare disease of the hair of the head which occurs in native women in the valleys of Cauca, in Columbia, and is characterised by the presence on the hair-shaft of from one to ten dark nodules about the size of nits. These nodules are as hard as stone, hence the name "piedra" (stone), and are seated on the side of the hair or form a concretion around it. When the affected hairs are combed these nodules cause a peculiar crepitant or crackling noise. The nodules are entirely outside the hair cuticle and cause no destruction of the hair itself, or splitting of the cortex into fibres such as occurs in trichorrhhexis nodosa, a disease with which piedra was at one time confused. Though usually affecting the hair of the scalp in native women, it has been observed also on the eyelashes and on the beard and hair of the head in men.

A microscopic examination of the nodules shews that they consist of masses of spores and hyphæ of a peculiar hyphomycetic fungus, which Juhel-Rénoy and Lion succeeded in cultivating on artificial media. The origin of this fungus is unknown, but it has been suggested that it may be connected with the mucilaginous fluid, resembling linseed oil, with which the native women in Columbia dress their hair. Under the heading of piedra nostras, Behrend and Unna have each reported cases of a similar affection in Germany, in which the hairs of the moustache were affected; and Trachsler, who made a series of cultivations of the fungus from both cases, shewed that although the two cases were indistinguishable clinically, they were the result of two different though closely-allied hyphomycetes. Mr. Malcolm Morris and Dr. Cheadle have also recorded a case of a peculiar nodular growth on the hairs of the beard

of a young man, to which they gave the name of *tinea nodosa*; and Dr Radcliffe Crocker has described a similar case affecting the hairs of the moustache. In these cases the concretions were composed of spores and mycelial threads cemented together.

The relation of Columbian *piedra* with these European cases is uncertain, and the varieties of hyphomycetes which are capable of causing the concretions on the hair have still to be worked out.

*Treatment* of *piedra* is similar to that employed for the softening and removal of nits (*vide* vol. viii 1899, p. 866). The scalp hairs should be soaked in a mixture of equal parts of crude paraffin and olive oil for about twelve hours. This can be done by saturating the hair with the mixture, covering the head with a nightcap for an hour, and then thoroughly washing with soap and hot water. This process should be repeated till the nodules have disappeared. Sponging the hair with hot corrosive sublimate lotion (1 in 1000) has also been recommended. In the case of *piedra nostras*, in which the beard or moustache is affected, frequent shaving or clipping should be employed, and a mild parasiticide, such as precipitated sulphur grs. xv., salicylic acid grs. x and vaseline  $\mathfrak{z}\text{i}$ , thoroughly rubbed in.

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**Madura Foot.**—Syn. *Mucetoma*, fungus-foot of India, *Mortuus tuberculis*, and various native names, such as *Shpuda* in Bengal, and *Hala Pura* in Deccan, designations which signify "large foot" or "elephant foot," *Kirina gah* or "dwelling of worms" in Rajputana, and *Galamma*, "egg foot," in Bellary (Scheube).

*Definition.* Madura foot is a disease of warm climates, principally endemic in India, usually affects the foot, and is characterised by swelling and deformity, with the degeneration of the affected tissues and the formation of cysts, with fistulous openings on the surface, containing an oily purrid fluid in which mycotic aggregations are suspended.

*History.* The earliest references to this disease are to be found in the writings of Kämpfer in 1712, but at that time it was confused with elephantiasis, and it was not till more than a century later that it was recognised as a specific disease by Godfrey in 1843, under the heading of "Tubercular disease of the Foot" (Manson). It is to Vandyke Carter, however, that we are indebted for the first detailed description of the clinical and anatomical features of the disease, and for the recognition of

granules as masses of fungus in the discharges. His extensive observations on the disease were published in a series of papers between 1860 and 1874. So thorough were the observations embodied in these papers that, except with regard to the parasitology and the geographical distribution of the disease, comparatively little advance has been made on the subject since, and subsequent observers have only corroborated and elaborated Carter's views upon it.

*Geographical Distribution.*—Madura foot is chiefly found in India, though it is not, as was originally believed, wholly confined to that peninsula. It is most prevalent in the western half of India, and when it occurs in the east it is believed to have been imported there. Its distribution is curiously limited to districts, the country between enjoying immunity from it. In the Madras Presidency, according to Hirsch, it is found in Madura—whence it takes its name,—Guntur, Bellary, Cochin, Ponnore, Trichinopoli, Pondicherry, and various other places. In the Bombay Presidency it is found on the slopes of the Western Ghats, Malabar, Karachi, Cutch, and Sind. In the Bengal Presidency it prevails in certain districts in Rajputana, Kashmir, and the Punjab; and in the North-West Provinces it is found in Sirsa and Hissar. It has been observed also in Colombo in Ceylon. In Africa cases have been reported from Egypt (Madden), the Sudan, Madagascar, Somaliland, Senegambia (Le Dantec), Morocco, and Algeria (Gémy and Vincent), and Jibuti on the Gulf of Aden (Bouffard). It has been observed in Canada (Adami and Kirkpatrick), in the United States, and in South America in Nicaragua and Chile. It has been found in the West Indies and Cuba. In Italy a case was recorded at Padua by Bassini.

The large number of cases which have been recently reported from different parts of the globe indicate that the disease has a distribution in tropical countries which is probably far wider than is known at the present time.

*Etiology.*—Madura foot is essentially a disease of agricultural districts, and attacks the bare-footed native labourers in the fields and plantations. It does not attack the European in India because of the better hygienic conditions in which he lives, and the protection afforded by the wearing of boots. It is more prevalent in men than in women, and chiefly about middle age. It attacks many of the native races, and the diverse latitudes in which it occurs prove that climate plays little part in its etiology. It is caused by the presence in the skin and underlying tissues of a *Streptothrix* closely allied to but differing from the ray-fungus of actinomycosis. The name *Streptothrix maduræ* has been given to it by Vincent. This fungus forms the fish-roe-like granules of the white variety, which is the common form of the disease. With regard to the fungus of the black variety there is considerable variance of opinion, some observers believing it to belong to a different species, while others (Hutchinson) regard it as a degenerative condition of the fungus of the white variety.<sup>1</sup> The latter opinion is most generally accepted, and is

<sup>1</sup>For a detailed description of the *Streptothrix* infections, see Vol. II. Part I. p. 302.

borne out by the occurrence of the black and yellow granules in the same case and also in different cases in the same district (Boccaro).

The precise habitat of the *Streptothrix Madura* is at present unknown. Though most probably it has a saprophytic existence, it has not yet been detected in the soil or in decaying vegetable matter. Its wide distribution, however, proves that it may be present in soils whose characters and flora are widely different.

Some abrasion of the skin is doubtless necessary to allow the fungus to penetrate the skin, such as may be caused by wounds, the bites and stings of insects, and pricks from the spines of plants. It has been suggested by Boccaro that in Sind the spines of a certain form of *Acacia* are responsible.

*Morbid Anatomy.*—On section the whole foot is found to have become softened and the tissues fused into a more or less homogeneous mass. It is easily cut through, and is then seen to contain a network of canals and cysts, varying in size from a pin's head to a pigeon's egg. These canals and cysts are connected, and open on the surface in funnel-shaped fistulous orifices. They are lined with fibrous tissue, and contain, in the white variety of the disease, cheesy masses of yellow or greyish granules like fish-roe; in the black variety dark brown friable masses like truffles (Manson); and in the red variety either pinkish aggregations or an oily fluid without granules (Lewis and Cunningham). These cysts are situated chiefly about the subcutaneous tissue, but are also found in the position of the muscles and of the bones, which have either disappeared or have become softened and beset with cavities.

*Microscopic* sections of the nodules, before they have softened, present an architecture recalling that of the foci of tuberculosis. They are the result of the reaction of the tissue to the presence of the streptothrix. In the centre of the nodule there is a mass of ray-fungus, which is oval or roundish in shape, or takes the form of a crescentic rosette. Surrounding the fungus there is a dense infiltration of small cells, consisting chiefly of leucocytes and small fibroblasts; more externally there is a layer of larger cells, made up of plasma-cells, connective-tissue cells, and a few giant-cells, with here and there some deposition of pigment; enclosing the whole is a layer or capsule of dense fibrous tissue. Around and between the nodules there is obvious inflammatory œdema of the tissue, with thickening of the walls of the blood-vessels and thrombosis. These nodules in the process of softening undergo various degenerative changes, which explain certain discrepancies in the description of the histology of the disease by the various writers on the subject (Kanthack, Boyce, Unna, Delbanco).

In tissue from a case of Madura foot I found that, when the nodule had softened, the granulomatous structure was replaced by a dense deposit of polymorphonuclear leucocytes and debris, in the midst of which were irregular aggregations of the fungus, and that plasma-cells, connective-tissue cells, and white fibrous bundles in a state of colliquative degeneration could be detected only at the periphery of the lesion.



*Symptoms.*—As indicated by its name, the foot is the part which is generally affected in this disease, and the right foot oftener than the left. Through some slight abrasion of the sole or other part of the foot, the primary inoculation takes place, and this results in the formation of an indurated circumscribed swelling about the diameter of a threepenny-piece. The initial lesion is comparatively rarely seen by the medical man, as the native either takes no notice of it or does not present himself for treatment till the disease is well advanced. The primary lesion runs an indolent course, and may or may not be associated with pain. After a couple of months it begins to soften and break down, gradually forming in the centre a fistulous opening, from which oozes a purulent, viscid, and oily discharge, in which granules of different colours, according to the variety of the disease, are suspended. The granules may be grey or yellow in colour like fish-roe, and vary in size from mere specks to aggregations as large as a pea; they may be brown or black, resembling coarse gunpowder; or in exceptional cases they may be red in tinge. Hence it is customary to divide this disease into three varieties, namely (1) the white, yellow or ochroid variety, (2) the black or melanoid variety, and (3) the red variety.

Gradually new nodules similar to the primary lesion appear, and undergo the same changes. These gradually increase in number, and render the skin of the foot irregular and tuberculated. They vary in size from a small shot up to a filbert, and are in different stages of evolution, some being solid, while others have softened or become converted into fistulous openings more or less blocked up by vegetations. The foot itself becomes greatly swollen and deformed. It becomes twice or three times as broad as in health, the sides become rounded, giving it an oval shape, the arch disappears, the sole becomes convex, and the toes raised up so that the patient is unable to place the heel and the toes on the ground at the same time. The ends of the fibula and tibia also become thickened, causing swelling of the ankle. To the touch the skin feels peculiarly elastic, and the whole foot gives the impression of a solid homogeneous mass. This is the result of a process of softening which has attacked all the tissues with the exception of the tendons and fasciæ, even the bones being invaded and becoming honeycombed with cavities. A probe introduced into one of the fistulous canals can generally be passed in all directions without meeting any definite resistance. The affected skin may be sensitive to the touch, but there is comparatively little pain in the disease, even when the probe is passed. Above the diseased area the leg becomes thin and atrophic, which is all the more noticeable in comparison with the swollen foot. The glands in the popliteal space and inguinal region may be enlarged, but this is not due to a metastasis of the disease, but simply to septic absorption.

The inevitable result is that the foot becomes useless, and the native is compelled to adopt some mode of locomotion which does not necessitate putting the foot on the ground.

Though in the majority of cases the foot is the part attacked, the

disease occasionally affects other regions such as the knee, hand, neck, and jaw.

The disease runs a slow course. At first it does not interfere to any extent with the general health of the sufferer, as it is a purely local affection, and does not invade the internal organs; but gradually from various secondary causes, such as septic absorption, anæmia, or poverty and starvation from loss of work, the patient, after a course of ten to twenty years, succumbs from exhaustion or some intercurrent disease. Nothing seems to stop the progress of the disease when once it has become established. Cases, however, have been recorded in which it has been arrested very early; two such instances of healing have recently been reported by Brumpt in cases of the black variety in Somaliland.

*Diagnosis.*—Occasionally the diagnosis of early cases of madura foot from elephantiasis, tuberculosis, syphilis, or leprosy may present some difficulties; but further observation of the case, the characteristic deformity, the presence of fistulous openings, and the discharge laden with mycotic aggregations, should serve to distinguish them easily. From actinomycosis the differential diagnosis may prove more difficult. Actinomycosis, however, is a disease which is transmitted from animals to man, and can be inoculated in animals; it occurs in temperate latitudes, often runs a rapid course, affects internal organs and mucous membranes, and has yellow granules in its discharges; madura foot is confined to man, has not been successfully inoculated in lower animals, occurs in the tropics, runs a slow course, does not become generalised, and presents granules of various colours.

The *treatment* of mycetoma is most unsatisfactory. In early cases the disease may possibly be arrested by cauterisation or excision of the initial lesion, but when the disease is well advanced partial or complete amputation is necessary, the incision being made through the healthy tissue beyond the lesion. The prognosis after extirpation is good with regard to recurrence, since the disease is local. Collas reports 116 successful results out of 127 cases, and only 2 relapses (Scheube). There is no specific medicinal treatment for the disease, and even iodide of potassium, of undoubted value in actinomycosis, seems to have little or no influence on madura foot.

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#### IV. Skin Affections due to Animal Parasites

*Animal parasites* play a more important part in the causation of skin affections in tropical than in European countries. This is explained not so much by climatic conditions as by the native's dirtiness, over-crowding, defective sanitary conditions, scanty clothing, and bare feet, which render him much more liable to infection than the European. Of the skin diseases due to animal parasites only three need be specially considered here; namely, *craw-craw*, *water-itch*, and those caused by the sand-flea or *jigger*.

**Craw-craw** is a generic name which has been applied indiscriminately both by white men and natives in West Africa to a variety of skin affection characterised by itching and more or less pustulation. Dr. O'Neil, who first employed the term in 1875, described under the heading of "**Craw-craw**" or "**Kra-kra**" a vesico-pustular affection, resembling inveterate scabies in its clinical characters and distribution. In the vesicles of it he detected a small filaria which he believed to be specific. Sir P. Manson subsequently recognised the filaria as the embryonic form of the *F. perstans* which is common in the countries where *craw-craw* is endemic, but he does not regard the filaria as being the cause of the disease. Dr. Bennett stated that the uneducated natives of Old Calabar gave the name *craw-craw* to practically all skin diseases, while the intelligent natives limited its application to three conditions, namely, leprosy or bad *craw-craw*, *tinea circinata* or *Krooboy's craw-craw*, and *craw-craw* proper, a papulo-vesicular disease which he believed to be a pustular eczema. Plehn has also described under this heading a papular dermatitis in natives on the Cameroon Coast, chiefly attacking the inside of the thigh. Emily has used the name on the French Congo, and applied it to a chronic pustular lesion which began as a reddish-brown spot, became excoriated by scratching and transformed into a superficial ulcer, the floor of which gradually became covered with pale granulations secreting a thick tenacious pus. A mosquito bite has been blamed for the production of the lesions, but it seems more probable that the mosquito bite or other abrasion gave entrance to some specific virus. Sir P. Manson has observed a similar affection in India and South China, and has noted the close similarity which it bears to *veld sores*. The above are a few of the applications of the term *craw-craw*, but there are many others, and, except as an interesting native name, it might well be abandoned.

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**Water-itch.**—Syn. *Coolie-itch, Ground-itch, Water-sore, Sori* (India; Assam, *Pani-ghao, Cutaneous ankylostomiasis*.

Water-itch is a form of vesicular dermatitis which attacks the feet of coolies working in the tea-gardens in Assam during the wet season. According to Dr. Elliot it is more prevalent in Upper Assam than in the provinces of Sylhet and Cachar. It has been described also in British Honduras (Browne), the West Indies, and the Southern United States (Smith), and has probably a much wider distribution.

In Assam after heavy rains as many as 5 per cent of the coolies may be incapacitated from work by this disease. It almost invariably attacks the feet, and only occasionally the legs. It begins with itching, followed by swelling of the feet, which gradually increases up to the second day, when walking becomes painful and the eruption appears. This consists of red macules or slightly raised papules, which rapidly become vesicles about the size of lentils. The lesions are situated either singly or in herpetiform groups about the sole, dorsum of the foot, or interdigital spaces (Elliot). The vesicles usually develop into pustules, and these in turn may form small ulcers, or in unfavourable circumstances through secondary inoculation become gangrenous. The affection is frequently associated with anæmia. In ordinary cases it is not a very serious disease from the patient's point of view, but it is of vast importance, for economic reasons, to the planter.

*Etiology.*—Water-itch occurs almost exclusively in the wet season, and is at its worst after a heavy rainfall, when the plantations are covered with liquid mud. The coolies working in the parts of the plantations near the habitations suffer more from the disease than those at work on the outside, and it is much more prevalent in the old plantations; a prevalence attributed to the greater contamination of the mud with human excrement near the habitations and in plantations which have existed for a number of years. Various suggestions have been made with regard to the cause of this disease. In 1901 Dr. Dalgetty described an acarus which he believed to be responsible for it; but this opinion is not generally accepted, and it is doubtful whether the acarus, to which the name of *Rhizoglyphus parasiticus* was given, is pathogenetic. Recently a new interest in the subject has been awakened by the experiments and discovery of Looss, Schaudinn, and others, that the embryos of ankylostoma are capable of penetrating the skin, and so producing ankylostomiasis. Bentley has asserted that he has produced an eruption of water-itch by rubbing into the skin

earth infected with the embryos of the *A. duodenale*. In the tea-gardens in Assam a large percentage of the coolies suffer from ankylostomiasis, and their excrement is impregnated with the ova. In the wet weather these are hatched, and the larvæ may easily penetrate the bare-footed coolies' skin, which is macerated and sodden from tramping about in the slush. In its passage through the skin the embryo is said to cause the eruption, and the ulceration and phagedæna which may supervene are regarded as the results of secondary pyogenetic inoculation. This attractive hypothesis requires further corroboration, however, before it can be definitely accepted (*vide* p. 898).

The *treatment* of the disease consists in daily bathing the feet in warm carbolic lotion (1 in 40), opening the vesicles and dusting on boro-iodoform powder. When open sores are present antiseptic dressings should be used. Until the feet have healed the coolie cannot work, and should be confined in the tea-garden hospital, for otherwise the treatment is apt to be a failure through want of co-operation of the patients. In several tea-gardens the coolies are made to wear "kurrams" or sabots with high heels at each end which raise the feet from the ground. Where these are in use the number of cases of water-itch has been largely reduced. Indeed, any protective covering for the feet is a preventive. In a recent communication Sir P. Manson refers to the use of green Barbados tar for this purpose in the West Indies, where it has proved of great value. Every morning the feet and legs of the coolies are painted over with the tar, and they are then made to walk through fine sand or sawdust, which adheres to the tar and forms an impermeable covering.

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The **Sand-Flea or Jigger**, *Sarcopsylla penetrans* (L.), was originally confined to tropical America and the West Indies, but was carried on ships from Brazil to West Africa, whence it spread rapidly, and now prevails in many parts of that continent.

The jigger is somewhat smaller than the ordinary flea (*Pulex irritans*) and inhabits sandy soil and the dust of native huts. It readily attacks any warm-blooded animal. It is the impregnated female which is responsible for the irritating eruption in man. The female (*S. penetrans*) burrows obliquely into the epidermis till only its posterior segment is visible, and there it remains, nourished by its host, till the ova

nature. It is visible as a small dark spot in the centre of a nodule or broken blister. Most commonly it attacks the soles of the feet, interdigital clefts, and the skin about the roots of the nails. Its presence is associated with irritation, inflammation, and occasionally suppuration; and from secondary inoculations the lesions may be the starting-point of phagedænic sores, erysipelas, and even tetanus. After the eggs mature they are expelled and fall into the ground, and the female jigger dies and shrivels up in the skin or is cast off.

The *treatment* consists in removing the insect, intact if possible, an operation which the natives become very skilful in doing. The small ulceration which is generally left is treated with antiseptic lotions or dusting powders. Should any portion of the flea remain it is advisable to touch the part with pure carbolic acid and dress the part subsequently with mercurial ointment. As prophylactic measures in districts where it occurs, the rooms and huts should be carefully swept to remove the dust which harbours the insect, the skin should be anointed frequently with oil of cloves, and the feet protected by stockings and sandals.

**Lesions produced in the skin by the larvæ of certain flies and the bites of ticks and leeches.**—In the tropics various types of local cutaneous lesions may result from the presence in the skin of the larvæ of certain flies, and from the bites of ticks, mosquitoes, certain large spiders, scorpions, and leeches. These lesions vary from wheals to painful suppurating sores, according to the character and virulence of the poison introduced by the bites. Of these special reference need only be made here to the lesions produced by the bites of ticks, and by the presence in the tissue of the larval stage of certain tropical flies.

**Myiasis** (from *μύια*, a fly) is a comprehensive name applied to the diseases caused by the presence in the tissues of the larvæ of certain flies. These flies deposit their eggs either on the skin or on the mucous membrane of the nose or external auditory canal; they are rapidly hatched, and the larvæ set up more or less serious pathological changes either in the skin and mucosæ or by boring down in the neighbouring tissues. (For an account of blood-sucking and other flies known or likely to be concerned in the spread of disease, see p. 169.)

The larva responsible for the most severe effects is the so-called “screw-worm,” which is the larval stage of a “blue-bottle” fly, known as *Lucilia macellaria* Fabricius, belonging to the family of the muscids. This fly occurs principally in South America, but it has also been encountered in North America, Cochin-China, and Tonkin (Depied). The larva is white in colour, measures about 14 mm. in length, and has a screw-like appearance owing to the presence on its surface of irregular rings of small horny spines. This fly attacks man as well as domestic animals, and deposits its eggs on the skin or on the nasal mucosa or auditory skin of natives sleeping in the open air. On being hatched the larvæ cause comparatively little harm in the skin beyond setting up a painful



; but when they occur in the natural cavities they generally enter into the surrounding tissues, passing through muscles, cartilages, and reaching the bones, and cause serious inflammatory disturbance. Frequently in such cases a fatal result may follow, either from sepsis or from the penetration of the larvæ into the brain and the production of meningitis. Of the larvæ which have their habitat in the skin the best known are the "Ver du Cayor," and the "Ver macaque."

"Ver du Cayor" is the larva of the *Ochryomyia anthropophaga* E. which is very prevalent in the Cayor district of Senegambia towards the end of the dry season. The genital organ of the female fly is provided with a small process by which the skin of man and various domestic animals is pierced, and in this abrasion the eggs are deposited. Certain writers have asserted, on the other hand, that the eggs are deposited on the skin and are hatched there, the larvæ getting into the skin subsequently (Scheube). The presence of the larvæ in the skin causes the formation of a small furuncle, which matures in about a week, breaks, and gives exit to a larva which is greyish-white in colour, composed of nine segments, and is about 12 mm. in length.

"Ver macaque" is the larva of a gad-fly, named the *Derma-niventrus* Macquart, syn. *D. norialis* Brauer, which is found in Central America, Mexico, and Brazil. R. Blanchard has shewn that the fly has two larval stages, the first, which is club-shaped and is known as the Ver macaque, and a further stage, which is worm-shaped and is called Berue or Torcel. When the larvæ are present in the skin they set up inflammatory swellings and abscesses, which may reach the size of a pigeon's egg, and have been termed "gad-fly boils." These readily break down and discharge a sero-purulent fluid containing the excreta of the larvæ. Skin-lesions of this type, produced by the bites of flies, have been reported from various countries, but the precise fly responsible in each has still in many cases to be identified. For example, cases have been recorded in British East Africa (Kolb), West Africa (Nagel), Lagos (Strachan), and also in the northern parts of Norway and the Shetland Islands.

*Treatment.*—The treatment of these lesions must be prompt and efficient. For the screw-worm affection, the diseased cavity should be washed with 1 in 20 carbolic solution, or swabbed out with pure carbolic. Should the larvæ have reached the frontal sinus, inhalations of formalin have been recommended to kill them (Jeanselme), and the sinus should be opened up to permit of free irrigation and the expulsion of the parasites. The boils resulting from the various larvæ in the skin should be treated on ordinary surgical principles and be freely opened, the contents being expressed, and should then be thoroughly irrigated. Finally, tobacco juice is allowed to trickle into the small opening which is usually present in the boils; this causes the larva to protrude, and should then be expressed (Scheube); a similar treatment is employed by the natives in Paraguay (Lindsay).

**Ixodiasis** is the term which has been applied to the affections caused in man and the lower animals by the bites of certain ticks (*Ixodes*). The ticks belong to the order *Acari*, of which the *Strigops* is a familiar member. The lesions caused in the skin by their bites are comparatively trivial. Certain of them, like the sheep tick (*Ixodes ricinus* Linn.), can penetrate the skin like the acarus of scabies, but the majority pierce the epidermis only with their probosces, and do not become imbedded. There is as a rule little discomfort from the bite of the tick, but soon afterwards an irritable wheal is formed, probably as the result of the injection of poisonous salivary fluid, and as the tick gorges itself with blood the irritation increases. As far as the skin is concerned the chief danger of tick bites is that they may be the seat of the secondary inoculation of pyogenetic micro-organisms or of the virus of certain diseases. On the other hand, the pathogenetic importance of the tick bite has recently been greatly emphasised by the proof that the tick is the intermediary host for the transmission of various serious febrile diseases, such as the "Miana" of Persia, and Human Tick fever (*vide* p. 301).

**Treatment.**—When the tick becomes fixed to the skin by its rostrum, it should be made to detach itself by putting a drop of turpentine or benzene on it; it should not be forcibly removed lest the proboscis be broken off and left in the skin. As preventive measures, the corners of rooms where ticks abound should be frequently sprayed with kerosene, and, if necessary, fumigated with sulphur, and precipitated sulphur should be dusted between the bed sheets. Instead of precipitated sulphur the powder of pyrethrum flowers has been employed for this purpose (Sambon).

For tick bites see p. 959

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#### V. Skin affections due to the Climate of the Tropics

Of the various skin affections which attack the white man in the tropics some are directly or indirectly dependent on the climate, and of these the most important are solar dermatitis or eczema solare and prickly heat or lichen tropicus.

**Prickly Heat.** For a description of this affection *vide* Vol. VII, 1899, p. 743.

**Solar Dermatitis** is an affection of the skin of the nature of acute eczema; it attacks the exposed parts, especially the face, and results from the irritation caused by intense sunlight. In mild cases, after a latent period of 6 to 12 hours after the exposure to the sun, the skin begins to smart and becomes hot and tense, and an erythema associated with slight oedema appears. Left to itself the inflammation usually subsides in about 48 hours and is followed by desquamation and transient pigmentation of the affected area. In severe cases the oedema is excessive and may go on to vesiculation, formation of bullae, and weeping. The loose tissue below the eyes becomes so oedematous that the eyes are almost closed up, and the pain may be as great as in erysipelas, for which the condition may be mistaken. In such cases about a week elapses before the inflammation disappears.

It has long been known that this affection is not the result of the heat rays from the sun, but is caused by the chemical or actinic rays at the violet end of the solar spectrum. This was pointed out as early as 1858 by Chareot, who demonstrated it experimentally, and his observations have been frequently confirmed. The dermatitis is not peculiar to the tropics, but may occur even in cold climates from the reflected light from snow-fields where the temperature is below zero and the heat rays have been eliminated. The degree of dermatitis depends on the intensity of the light and on the type of skin of the individual affected. Dark races do not suffer from it, as their skin is protected by pigment, which prevents the penetration of the powerful actinic rays. Where the sunlight is most intense the native is most deeply pigmented. In Central Africa, for example, the native is almost jet black: farther away from equatorial sun, as in Abyssinia, he becomes dark brown; in Morocco a lighter brown, in Southern Europe olive, in Central Europe brunette, in Scandinavia blonde. The actinic rays stimulate the skin, causing the production and deposition of pigment granules in the deeper layers of the epidermis. For this reason the European becomes bronzed after a comparatively short residence in the tropics. Great interest has recently been aroused on this subject by the researches of Finsen, and the application of the actinic rays in the treatment of tuberculosis of the skin and various other affections. In this form of treatment an inflammatory reaction is artificially produced by actinic rays obtained from a powerful arc lamp, and the reaction is the same as occurs in an acute solar dermatitis. This inflammatory reaction causes an oedematous degeneration of diseased tissue, and in the subsequent process of repair replaces it by new fibrous tissue and a healthy scar.

*Treatment.*—In an acute attack of solar dermatitis soothing treatment is indicated. When the erythema and oedema are severe a lead lotion, consisting of half a drachm to the ounce of the liquor plumbi subacetatis in water or milk and applied continuously in the form of a compress or on a lint mask, is of great service. Under this treatment the inflammation quickly subsides. If vesicles or blisters be present, care must be taken to prevent them becoming septic. Should this occur it is advisable to

apply boric acid compresses and dressings of boric acid ointment instead of the lead ointment. After the inflammation has gone down the skin tends to peel and become pigmented. The pigmentation gradually disappears, and desquamation can be counteracted by the application of cold cream. Of course, in all cases, however mild, confinement to the house when the sun is up is essential. Much can be done to prevent solar dermatitis in the tropics by suitable headgear, parasols, and veils. These should be orange or red in colour and not white or green, since red materials allow only the harmless red rays to penetrate and are opaque to the actinic rays.

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## VI. Dystrophies

**Vitiligo.**—Complete albinism with pink eyes and white hair is rare in dark-coloured peoples, but partial albinism or vitiligo is more common than in white races. It is possible, however, that, as it is much more noticeable in dark skins, it appears to be more prevalent than it really is, while in white races mild degrees of it may not attract attention. Besides typical vitiligo non-pigmented patches in which the pigmentation gradually reappears may occur in association with syphilis, or, when desquamation has taken place, in various native hyphomycetic affections, such as *tinea imbricata* and *caraté*. Vitiligo in the native has to be distinguished from the whitish patches of anæsthetic leprosy, a condition with which it has frequently been confused. (For a detailed description of vitiligo see Vol. VIII., 1899, p. 706.)

**Cheloids and Hypertrophic Scars.**—Though cheloids and hypertrophic scars may occur in any climate and may affect any race, they are unusually prevalent in dark skins. In the negro they are prone to follow slight injuries, abrasions, stings and bites of insects, vaccination, and the sores of leprosy, tuberculosis, and syphilis. Le Dantec and Boyé report a case of fibromatous growths or “keloidal fibromata” growing in the lobes of the ears of negroes after being pierced for ear-rings; and various other writers have recorded cases of an allied nature. Various peoples, such as certain of the tribes in Oceania and the Australian aborigines, adorn themselves with hypertrophic scars as other races do with tattoo-marks: these they produce by cutting themselves with some sharp edge, such as a piece of flint or a broken shell, and rubbing grass or mud into the open wound. The hard and fast distinction which was once drawn between the so-called spontaneous cheloid and ordinary scar-cheloid, and on which Kaposi insisted, is gradually giving place to the view that pathologically both types are variants of the same process and that possibly they both result from the inoculation of some micro-organism. This suggestion—

for it is only a hypothesis at present, since no such microbes have yet been established—would readily explain the great frequency of cheloidal growths in dark-coloured natives, in whose unprotected skins so exposed to injury secondary inoculation of wounds and abrasions by a number of micro-organisms is the rule rather than the exception. (For a detailed description of cheloid see Vol. VIII., 1899, p. 685.)

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### LATAH

By SIR PATRICK MANSON, K.C.M.G., LL.D., M.D., F.R.S.

AMONG the natives of the Malay Peninsula, of Java, and of the neighbouring islands—in some localities more than others—examples of a peculiar mental affection, locally known as Latah (a word signifying nervous or ticklish), are not uncommon. It occurs more frequently in women, especially young women, than in men; children are rarely affected. It persists for years, and is seldom recovered from.

Although there may be considerable variety in the particular symptoms and in their intensity, in all instances the characteristic features of this psychosis are the same; they depend on an abnormal and exaggerated susceptibility to the influence of suggestion.

In ordinary circumstances the subjects of latah appear in no way different from their neighbours. But on the occurrence of some sudden and startling impression, such as a loud sound or anything calculated to produce a vivid impression, or on witnessing particular movements, or on hearing particular sounds, or in response to some overt suggestion by word, movement, or facial expression on the part of an experimenter, they pass into a peculiar mental state in which they involuntarily utter certain sounds or words or execute certain movements. In other instances they will imitate words and movements, or yield themselves to suggestions coming from others or even from the phenomena of external nature. During this hypnotic-like state, which in some may last for a few moments, in others for an indefinite time or until removed by a contrary suggestion, although consciousness and intellect are clear, and although strenuous effort may be made to resist suggestion, the victim is at the mercy of his prompter, and will inevitably follow any lead indicated, no matter the consequences.

Although the manifestations of high degrees of latah may be followed

by signs of exhaustion, and even by swooning, as a rule nothing of the kind occurs. There are no stigmata by which these people can be recognised. Their infirmity is discovered by accident. Subsequently, although the fact that a particular individual is latah soon becomes known to the neighbours, it is not held to disqualify him for employment in any ordinary capacity.

Sir F. Swettenham, basing his description on personal experiences, gives a graphic account of this disease. At one time he was in command of a small body of native police, two of whom were latah. To pass the time the companions of the latah-struck men amused themselves by taking advantage of this circumstance. On one occasion an inspector saw one of the latah men on the top of a cocoa-nut tree. On being asked what he was doing there, the man replied that he could not come down because there was a snake at the bottom of the tree. In reality there was a bit of rattan round the stem; on this being removed the man came down without hesitation. The inspector ascertained that the other police had ordered the latah man to climb the tree; this he did, and then, out of sheer devilry, some one taking in his hand a rattan, and saying, "Do you see this snake? I will tie it round the tree, and then you can't come down,"—tied the rattan round the tree. The man was there from 10 A.M. till 4 P.M. "Speaking generally," Sir F. Swettenham says, "it was only necessary for any one to attract the attention of either of these men by the simplest means, holding up a finger, calling them by name in a rather pointed way, touching them, or even, when close by, to look them hard in the face, and instantly they appeared to lose all control of themselves, and would do, not only whatever they were told to do, but also whatever was suggested by a sign." Thus, at the word of command, or even on witnessing an action suggestive of a dive, they would plunge into a river regardless of the danger from crocodiles. If told to strike another man they would do so; and if the person struck resented the blow, they would say, "It is not I who hit you, but that man who ordered me." On another occasion one of these men on being told that a roll of matting was his wife embraced it with every sign of affection; and when the other latah policeman was informed that the same roll of matting was his wife likewise, he too embraced it, and the two men fell to the ground struggling for possession of the lady. Similar stories are current about latah people throughout the Malay country.

Not unfrequently the latah man or woman, if startled by an unexpected touch, noise, or sight, will not only shew all the signs of a very nervous person, but, almost invariably, will fire off a volley of obscene expressions having no reference whatever to the particular circumstances of the moment. As a rule, in order to find out that they are latah, it is necessary to startle them. They are conscious of their infirmity, and in most instances dislike and try to avoid its manifestation.

Latah folk are favourite subjects for the practical joker. Children and even grown-up people cannot always resist the temptation to hit them; for one reason because it is exceedingly easy to do so, for



other, because these unfortunates are inclined, on the spur of the moment, to do ludicrous things or to say something of which, in ordinary circumstances, they would be ashamed. Fortunately for their tormentors, latah people are generally good-humoured and rarely resent such liberties; in a few instances, however, they object to being made show of and may become dangerous.

**Pathology.**—Latah seems to be akin to a class of emotional diseases which, in their kinds, are common in all barbarous and semi-civilised countries; nor are they wanting among the superstitious and weak-minded of more advanced nations. Among the many forms of this type psychopathy there are several which closely resemble the latah of the Malays; such, for example, is an affection prevalent among the Amoyeds, known as “ikota.” According to Schrenk, ikota is confined to married women. In its milder form it declares itself by inarticulate sounds which are emitted whenever the affected person sees something repugnant to her, or if she is teased about her peculiar susceptibility. In its more severe form the patient becomes temporarily maniacal, assuming the appearance of sanity when the paroxysm is over. In latah, and in ikota, the individual manifestations are induced in similar ways; both they are paroxysmal, evanescent, and recurring; and in both the liability to the attacks is more or less permanent.

To the same class of psychopathies belong such affections as the “possession by devils” of the ancient Syrians, and the “tigretier” or the “boudda” disease, and “zarr” of the modern Abyssinian. Such-like psychopathies are by no means confined to one or two peoples; wherever there is a lively belief in the existence of a personal devil, or of evil spirits, or in the possibility of “possession,” there, under a variety of local names, these and like maladies are sure to be found.

Allied to, but somewhat differing from, these are those curious epidemics of religious ecstasy which, during the Middle Ages, swept over many parts of Europe, and which, even in modern times, are apt to break out during what are known as “seasons of revival.” Such were the dancing frenzy and the children’s crusades of mediæval Germany; the tarantism of Italy of the fifteenth and seventeenth centuries, the “preaching disease” of Sweden; the “jumpers” of Cornwall; the “barkers” of the United States; the eccentric sects of Russia, and many similar absurdities, which have been and are perpetrated under the names of religion or freedom.

These religious and social epidemics differ somewhat in their essence, as well as in their course, from the type of psychopathy represented by latah and ikota. In the case of latah the individual attacks are sudden in their manifestation, supervening immediately on the inducing shock or suggestion, are not voluntarily induced or sought for, and cannot be controlled; moreover, the condition may be permanent and is not readily communicated to large numbers. In the religious and social psychopathies the morbid condition is more evanescent, it supervenes gradually, may be voluntarily induced, is often voluntarily sub-

mitted to, can often be controlled, and is readily communicated to large numbers. Latah and the like seem to be diseases of the intellectual reflexes; the religious and social psychopathies are rather diseases of the emotions. The former may be said to behave as an endemic disease, the latter as an epidemic. This dissimilarity in their natural histories depends, probably, on underlying differences in the psychical elements involved.

These differences apart, such psychopathies have many points in common. In none of them is there any gross physical lesion. Unless by accident they are not fatal. In all of them there is an underlying and personal emotional temperament; an implicit belief in certain superstitions; a strongly marked susceptibility to the influence of example, with a corresponding impulse to imitate; and, most probably in some instances, at all events in the early stages, a hysterical craving for sympathy, a desire to excite curiosity or wonder, or a wish for a certain kind of personal distinction. Possibly in some cases of latah there may be nothing of this kind, or no consciousness of it; but undoubtedly in many instances hysteria plays a part in the earlier stages. What at first may have been a bad habit only crystallises by and by into second nature; a consummation which may be further led up to by a desire to appear consistent and to live up to an acquired reputation.

The particular form these psychopathies assume depends in great measure on the superstitions and customs of the country in which they occur, and on contemporary ideas and influences. Hearsay, tradition, and example determine, as a rule, the endemic types much in the same way as they determine the national or local methods of revenge or of suicide. Thus, whilst the disgraced and despairing Englishman will shoot or hang himself, the Japanese in similar circumstances will rip his belly open, the Malay run amok. So custom contributes to determine the fashion of the Abyssinian tigretier, the Samoyed ikota, and the Malay latah. In the case of the religious and social epidemic psychopathies the particular form assumed will depend in a measure on the fashion set by the originating apostle, or, perhaps, on the plans of designing leaders.

In the religious psychopathies the emotional exaltation, though in the first instance confined to purely spiritual matters, tends to spread to other emotional centres, and may thus lead to wild sexual and even homicidal orgies.

Gimlette calls attention to the medico-legal aspects of this disease. Fortunately, examples in which latah has been shewn to play a part in crime are rare or unknown. It is conceivable, however, that under the influence of suggestion an affected person might be induced to kill, or commit some other crime. In such circumstances it might be difficult to assess or to fix responsibility.

**Treatment.**—Of the various forms of “possession,” latah is one of the most rebellious. Devils, spirits, and wild beasts may be exorcised by the resources of priest-craft, by music, by drugs reputed to have

special virtues, by other strange and often repulsive means—in other words, by an appeal to those superstitious and emotional elements that raised them. Latah, however, has the reputation of being incurable ; the reason for this special rebelliousness is not easily discerned.

The prophylaxis of these psychopathies, whether endemic or epidemic in type, manifestly lies in judicious mental and physical education.

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## INSOLATION OR SUNSTROKE

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UNDER the designation of sunstroke, heat-stroke, insolation, thermic fever, calenture, heat apoplexy, heat asphyxia, ictus solis, and other synonyms, a number of morbid conditions, from the simplest to the gravest, are included. However these conditions may be modified by personal susceptibility, local surroundings and climatic influences, they are all essentially due to heat, and are the result of exposure either to the direct rays of the sun or to a high atmospheric temperature in the shade.

Great heat may cause—

1. A state of exhaustion leading to syncope.
2. An overheating of the nervous centres, blood, and tissues ; with a tendency to produce vasomotor paralysis, hyperpyrexia (thermic fever), and subsequent asphyxia through the action upon the respiratory centres. Herewith lesions may take place, such as cerebral tissue-change and hemorrhage, and meningitis in various degrees. The symptoms in such cases are varied, and depend upon the portions of the cerebrospinal centres affected.

The effect of heat upon the human body in tropical climates or elsewhere is a subject of considerable importance and interest. Man, of all animals, possesses the greatest power of adapting himself to and maintaining health under changes of climate and temperature. His body, in favourable circumstances of climate, food, and habits, has the power of maintaining an almost constant temperature under extremes of heat

and cold. Vigorous healthy persons, who lead temperate and well-regulated lives, can tolerate a very much higher temperature than those not so conditioned, and the natives of tropical climates—especially the coloured races—can tolerate an amount of heat to which the European would succumb even they, however, suffer at times if the heat rise above a certain point, and natives of India frequently die from 'ho marna,' hot wind-stroke.

The action of heat is much influenced by the hygrometric condition of the atmosphere. A dry hot air is better tolerated than a moist one at a lower temperature, because it favours perspiration and keeps the body cool, while damp air diminishes evaporation and the refrigerating processes of the body. When, from any cause, perspiration, i.e., glandular secretions or the natural eliminative functions are interrupted, especially when the air temperature exceeds that of the normal heat of the body, suffering soon ensues, and danger from ardent fever or heat asphyxia becomes imminent. That these evil consequences are not due to the direct action of the sun alone is shewn by the fact that many of the fatal cases take place in rooms, tents, or hospitals, at night or in the early hours of the morning before sunrise, especially if the air is vitiated as well as hot—previous disease, debility, or irregular and intemperate habits, dispose to insolation.

The effects of all the conditions of hot climates, including heat, are not yet sufficiently determined, and we must look for further information to medical men practising abroad. Continued exposure to great heat cannot long be endured, even by the healthy human body, with impunity. Parkes and others have shewn its injurious effects on the nervous system, on secretion and elimination, and on the digestive and assimilative processes. It causes fever from the simplest to the most ardent form, and it is often combined with pernicious miasmatic poisoning, extreme cases of which may be confounded with or pass into the most aggravated forms of thermic fever or asphyxia.

Insolation generally takes place in the hottest months of the year. April, May, June, and July give the highest returns in India—but whenever the temperature is high enough in other countries the same results obtain. For example, it is very frequent in North America every year.

It has been stated that sunstroke seldom, if ever, occurs at sea—but this is negated by the records of vessels passing through the Red Sea, Indian Ocean, Persian Gulf, and other tropical seas. I have myself witnessed death on board steamers in the Red Sea from insolation. Maclean tells us, among other examples of insolation occurring on board ship, that Boudin relates that, while at Rio Janeiro, the French war-ship *Duquesne* had 100 cases of insolation out of a crew of 1200. Most of the men were attacked, not when exposed to the direct rays of the sun, but at night when in the recumbent position—that is, when breathing not only a hot and suffocating, but also an impure air. Basset gives an account of 18 cases out of a crew of 78 men, which happened on board the man-of-war brig *Le Lynx*, cruising off Cadix in

August 1823. The heat, aggravated by calms, was excessive—91 to 95° F. the vessel small and overcrowded.

It is hardly possible to fix any particular degree of external temperature as one of excessive danger, because, as before stated, the tolerance of heat is very great in persons in perfect health in a pure atmosphere, and also in the dark skinned races; but, under the conditions before mentioned, the danger is great when the temperature is equal to or higher than that of the body. A temperature of 110° or 115° F. or higher, in very dry air in motion, would be better tolerated than one of 90° or 95° F. in an atmosphere laden with moisture; especially if it be vitiated, as in barracks or rooms, by human respiration, or telluric or other miasmas.

All who suffer do not die; some recover perfectly, but many are permanently injured, and made unfit for service in a hot climate, or even become permanent invalids at home.

In 1891 the numbers of the European army in India were 67,030. Of these there were 228 admissions from heat-stroke and 65 deaths.

In 1892 the numbers were 68,162. There were 223 admissions from heat-stroke and 61 deaths.

In 1891 there were 3137 women with the European army. Among these there were 2 admissions and 2 deaths from heat-stroke.

In 1892 there were 3101 women with the army, but no admissions from heat-stroke; one death out of hospital.

In 1891 there were 5886 children with the European army. There were 3 admissions and 2 deaths from heat-stroke.

In 1892 there were 5762 children with the army. There were 4 admissions and 4 deaths from heat-stroke.

The Native army in 1891 numbered 128,600. There were 22 admissions and 12 deaths from heat-stroke.

In 1892 the Native army numbered 145,340. There were 43 admissions and 18 deaths from heat-stroke.

In 1891 the jail population of India numbered 101,019. There were 77 admissions and 40 deaths from heat-stroke.

In 1892 the numbers were 103,159. There were 77 admissions and 41 deaths from heat-stroke.

The above numbers shew that the admission rate per mille from heat-stroke in the European army in India was, in 1891, 3·4; in 1892, 3·3; while the death rate in 1891 was 0·97; in 1892, 0·90. Among the women with the European army the admission-rate in 1891 was 0·64, in 1892, 0; while the death rate in 1891 was 0·64; in 1892, 0·32. Among the children the admission rate in 1891 was 0·5, in 1892, 0·7; while the death-rate in 1891 was 0·34; in 1892, 0·35. In the Native army the admission rate in 1891 was 0·2, in 1892, 0·3, while the death rate in 1891 was 0·09; in 1892, 0·14. Among the jail population the admission-rate in 1891 was 0·8; in 1892, 0·7; while the death rate in 1891 was 0·40; in 1892, 0·40.

\* The one death was out of hospital.

The following statistics and tables are taken from the reports of the Sanitary Commissioner with the Government of India for 1891 and 1892 :—

Deaths from Heat-stroke in the European Army in India in 1891 and 1892 at the different Ages.

Age.	1891.	1892.
24 and under . . . . .	35 or 1·06 per mille	26 or 0·76 per mille
25 to 29 . . . . .	14 or 0·58 „	21 or 0·84 „
30 to 34 . . . . .	8 or 1·41 „	9 or 1·65 „
35 and upwards . . . . .	7 or 3·33 „	5 or 2·40 „

Deaths from Heat-stroke in the European Army in India in 1891 and 1892 at the different periods of Residence.

Length of Service.	1891.	1892.
First and second years . . . . .	36 or 1·74 per mille	23 or 1·00 per mille
Third to fifth year . . . . .	18 or 0·59 „	22 or 0·72 „
Sixth to eighth year . . . . .	5 or 0·43 „	12 or 1·03 „
Eleventh to fifteenth year . . . . .	3 or 1·81 „	2 or 1·40 „
Fifteen years and upwards . . . . .	2 or 3·27 „	2 or 3·85 „

I am indebted to the Director-General of the Army Medical Department, Surgeon-General Keogh, K.C.B., and to the President of the Indian Medical Board, Surgeon-General Branfoot, C.I.E., for the following additional information relating to the years 1901, 1902, and 1903. Surgeon-General Branfoot, in reference to the year 1901, quotes the following remarks extracted from the Report of the Sanitary Commissioner with the Army of India :—“The heat-stroke death-rate for India rose, the greatest shares of the increase being in Madras and the Punjab. Nowgong, Meeanmeer, and Benares had the highest admission ratios, and Meeanmeer and Meerut the highest numbers. The ratios of mortality from heat-stroke are highest after thirty years of age, and in the earliest and latest years of service in India. No remarks of etiological interest are made by medical officers. Washbourn reports that in South Africa he never saw or heard of a well-marked case of heat-stroke, and considers this to shew that something more than the actual heat of the sun is necessary for the production of the disease, and to support the view that the disease is due to some infection. Griffin has published an interesting case of heat-stroke occurring at sea, and Schmidt has written ably on the subject.”

In 1901 the numbers of the European army in India were 60,551. There were 174 admissions and 40 deaths from heat-stroke.

In 1902 the numbers of the European army were 60,540. There were 171 admissions and 46 deaths from heat-stroke.



In 1903 the numbers of the European army were 69,613. There were 303 admissions and 53 deaths from heat-stroke.

In 1901 there were 2908 women with the European army of India. Among these there were 1 admission and 1 death from heat-stroke.

In 1902 there were 2555 women with the European army. There was 1 admission and no deaths.

In 1903 there were 2891 women with the European army. There were 5 admissions and 2 deaths from heat-stroke.

In 1901 there were 5376 children with the European army. There were 4 admissions and 1 death from heat-stroke.

In 1902 there were 4709 children with the European army. There was 1 admission and no death from heat-stroke.

In 1903 there were 4677 children with the European army. There were 3 admissions and 2 deaths from heat-stroke.

In 1901 the Native army in India numbered 141,727. There were 32 admissions and 5 deaths from heat-stroke.

In 1902 the Native army numbered 142,886. There were 17 admissions and 4 deaths from heat-stroke.

In 1903 the Native army numbered 142,435. There were 22 admissions and 13 deaths from heat-stroke.

In 1901 the jail population numbered 121,811. There were 128 admissions and 73 deaths from heat-stroke.

In 1902 the jail population numbered 114,334. There were 112 admissions and 29 deaths from heat-stroke.

In 1903 the jail population numbered 101,717. There were 129 admissions and 40 deaths from heat-stroke.

Surgeon General Sir A. Keogh gives the following statistics of the incidence of heat-stroke among the European troops stationed at home and abroad for the years 1902 and 1903 —

In 1902 in the United Kingdom there were 14 admissions, no death. In Gibraltar, Canada, Bermuda, Barbadoes, West Africa, Mauritius, and the Strait Settlements there were no admissions. In Malta there were 2 admissions and 1 death. In Egypt and Cyprus there were 2 admissions. In Jamaica 3 admissions and 1 death. In South Africa 2 admissions. In Ceylon 7 admissions and 3 deaths. In China 2 admissions. In India 171 admissions and 46 deaths. On board ship 39 admissions and 1 death. Total, 242 admissions and 52 deaths.

In 1903 in the United Kingdom there were 6 admissions. In Gibraltar, Canada, Barbadoes, Jamaica, West Africa, and Mauritius there were no admissions. In Malta there were 4 admissions, no death. In Egypt there were 4 admissions and 2 deaths. In Bermuda 2 admissions, no death. In South Africa 43 admissions, no death. In Ceylon 11 admissions, 2 deaths. In China 4 admissions. In the Straits Settlements 6 admissions, 4 deaths. In India 303 admissions, 53 deaths. On board ship 2 admissions, no death. Total, 385 admissions and 61 deaths.

Deaths from Heat-stroke in the European Army in India in 1901, 1902, and 1903 at the different periods of Residence.

Length of Service.	1901.	1902.	1903.
Under 1 year . . .	3 or 1·04 per mille	15 or 1·73 per mille	23 or 1·23 per mille
1 and up to 2 years . . .	6 or 1·62 „	5 or ·92 „	8 or ·78 „
2 „ 3 „ . . .	8 or ·77 „	2 or ·31 „	3 or ·38 „
3 „ 4 „ . . .	6 or ·63 „	3 or ·33 „	1 or ·16 „
4 „ 5 „ . . .	2 or ·23 „	4 or ·48 „	4 or ·50 „
5 „ 10 „ . . .	12 or ·76 „	12 or ·80 „	11 or ·92 „
10 years and upwards . . .	3 or ·12 „	2 or ·63 „	3 or ·92 „

Deaths from Heat-stroke in the European Army in India in 1901, 1902, and 1903 at the different Ages.

Age.	1901.	1902.	1903.
Under 20 . . . . .	...	...	...
20 to 25 . . . . .	14 or ·54 per mille	10 or ·45 per mille	23 or ·72 per mille
25 to 30 . . . . .	14 or ·55 „	23 or ·97 „	20 or ·87 „
30 to 35 . . . . .	5 or ·91 „	6 or ·96 „	5 or ·72 „
35 to 40 . . . . .	5 or 3·33 „	4 or 2·5 „	3 or 1·61 „
40 and upwards . . . . .	2 or 3·91 „	...	2 or 4·94 „

The statistics shew how the effects of heat influence a certain class of persons who are under hygienic control ; reliable data thus being afforded on which to determine the value of this element of the death-rate of a certain section of the population whose vital statistics are trustworthy. In others less protected, as in the scattered European, Eurasian, and immense native population, the incidence of the disease is often greater. In seasons when there are great accessions and waves of heat all over the world the disease and the mortality from it increase. Such waves of high temperature recur at uncertain intervals. No doubt the same obtains in other countries where the climatic conditions are similar ; it is needless, therefore, to produce further statistics, as these sufficiently illustrate the subject.

A number of cases of hemiplegia are reported by the Sanitary Commissioner with the Government of India, which there is reason to believe were also due to attacks of insolation ; but as it is not certain that all were so caused, I am content to allude to it generally as one of the possible results of sunstroke.

**Symptomatology and Pathology.**— In addition to the general disturbance of health which occurs in all who are more or less affected by heat — such as restlessness, irritability, sleeplessness—the morbid conditions which are to be attributed to the effects of a high temperature are :—

I. A. Syncope from exhaustion, caused either by the direct rays of the sun or a heated atmosphere in the shade, especially when the physical or mental powers are depressed. Engine-room men in steamers in hot climates; men marching, or on parade, if oppressed with clothes or accoutrements, or weakened by previous illness, or by dissipation; labourers or artificers; men in hay-fields in England, or in heated rooms and factories, in barracks, hospitals, tents, or ships, may suffer in this way. The condition is one of depression; the skin is cold and pale, and the pulse feeble. Death may occur from failure of the heart, but recovery is usual.

B. The exhaustion above described having passed away may be succeeded by fever, which may assume an ardent type. The fever may, after a certain duration, defervesce; or it may result in changes, the consequence of damage done by the heat to the cerebrospinal centres. Thus a variety of morbid conditions may ensue, depending upon the parts affected. Such cases are often very prolonged, and the only hope of recovery lies in removal to a colder climate.

When death occurs rapidly at the time of the exposure it may be due to sudden cardiac failure, as shewn in the experiments of Claude Bernard and Sir Lauder Brunton upon animals exposed to great heat. When it occurs suddenly, during great exhaustion or muscular action with fatigue, it may be due to coagulation of the cardiac myosin, which Dr. Wood of Philadelphia has shewn to be likely to occur during any great muscular exertion at a much lower temperature than usually determines it when there is no great muscular exertion. For example, men fighting in a very high temperature may fall dead suddenly; but perhaps coagulation of myosin is most frequently a post-mortem change.

II. The gravest and perhaps most fatal forms of sunstroke occur as a consequence of the general heating of the whole body, blood and tissues, which may happen either from prolonged exposure to the sun's rays in a heated atmosphere, to a heated atmosphere in the shade (occurring, as it does, by night as well as by day), or to an abnormal thermotaxic state due to vasomotor or other heat-regulating disturbance.

In the first case the effect of the high temperature tells upon the brain, which becomes heated to a degree incompatible with due performance of its functions: this may result in acute cerebral symptoms, and sometimes in mania, rapidly passing into a state of asphyxia, if the respiratory centres are involved: more frequently, perhaps, the whole body becomes overheated, the temperature rising to 106°, 108°, or 110° F. which, if not rapidly counteracted, proves destructive to life by asphyxia or sudden cardiac failure, or even by cerebral hæmorrhage or meningitis.

In heat-exhaustion the primary symptoms are those of depression. The person becomes faint, pallid, with a cold and moist skin and feeble pulse, not unfrequently attended with sickness. The soldier on parade staggers and falls over in a faint; so with the orator when speaking, or

the artisan in pursuing his calling. This may take place either in the sun or in the shade. The condition is one of syncope, and may approach collapse; if reaction be not soon established death may result from cardiac failure, but this is rare. Recovery is generally complete, but when the state has occurred from direct application of intense solar heat and glare, the mischief is not always confined to the transient shock or impression; secondary effects, such as vertigo, muscular tremors, and temporary loss of power may result; or a reaction may be followed by fever, by symptoms indicating lesions of the centres, or by cerebral excitement, and this may end in mania.

In insolation proper the premonitory symptoms may appear some hours or even days before the dangerous symptoms set in, as the result of continued exposure to a high temperature; although they may occur also in a much shorter period, as when men are exposed in marching or in other occupations to a very high degree of solar heat, in which case some would no doubt be affected by heat-exhaustion, whilst others would pass into a state of hyperpyrexia as before described. These are generally malaise, restlessness, insomnia, apprehension of impending evil, precordial anxiety; hurried, gasping, shallow breathing; a feeling of constriction round the thorax; vertigo; headache, often severe; nausea, or even vomiting, anorexia, great thirst, frequent micturition, and fervent heat of the skin. As one or more of these symptoms become aggravated the temperature rises to  $104^{\circ}$ ,  $106^{\circ}$ , or even  $110^{\circ}$  F. Dyspnoea and restlessness increase; the head, face, neck, and skin of the body generally become red or livid, sometimes dry, sometimes moist; the pulse full and labouring, carotid pulsation very perceptible, pupils contracted, but dilating widely before death. Unconsciousness passes into complete coma, stertor, and epileptiform convulsions; finally, relaxation of the sphincters and suppression of urine precede death.

These symptoms all indicate a profoundly disturbed state of the cerebrospinal centres and a disordered condition of the blood. The hyperpyrexia is incompatible with a due performance of their functions, and death will rapidly result unless prompt aid be given; indeed, it frequently does so despite all treatment. The fatal result is due to asphyxia and cardiac failure. There may be—though perhaps rarely—meningitis or cerebral hæmorrhage or effusion, the disordered state of the blood not unfrequently manifesting itself by petechial patches on the body.<sup>1</sup>

The earlier stages of this condition are those of so-called thermic fever. A very high temperature may be maintained for several days, and finally defervescence takes place without evidence of any structural lesion; but unless active measures be used and the temperature rapidly reduced,

<sup>1</sup> I have read again with much attention Dr. Sambon's thoughtful and interesting communication. Notwithstanding the evidence he produces and the arguments he brings forward, which are entitled to much respect, I do not see any reason for modification of the views here expressed on the subject of sunstroke, nor any fresh grounds that would justify me in referring the various and complex symptoms that characterise that condition to an organism growing in the soil, rather than to the effects of climate and temperature.

unless, that is, the causes which produce the hyperpyrexia be mitigated or removed, the case is apt to pass on into the grave state, and to terminate fatally by paralysis of the respiratory centre, and in some instances, though rarely, by cerebral hæmorrhage. From the graver forms some recover, but many are permanently injured, and become invalids for life; life indeed is not unfrequently shortened by obscure cerebral or meningeal changes which affect the sufferer in varying degrees of form and intensity, such as epilepsy, irritability, impaired memory, cephalalgia, blindness, or deafness, partial or complete paralysis, dementia or even mania. In those who have apparently recovered, intolerance of the sun's rays or even of the heat of temperate climates may remain; or such cases may after a long time end in dementia, or epilepsy, or both; or in chronic meningitis with thickening of the calvaria; frequent or intense headache, general functional derangement and disordered innervation being persistent.

**Morbid Anatomy.**—When death has occurred in the syncopal form there is not any very obvious morbid change. The brain with its membranes and the lungs are sometimes but not always congested. The venous trunks in the abdomen and also the right cavities of the heart may be full of blood, which is imperfectly coagulated. The abdominal viscera are congested; lividity of the body and decomposition come on rapidly after and even before death.

In death from thermic fever and insolation the heart is sometimes found firmly contracted—it may be from coagulation of the myosin and the venous system generally is engorged. The blood is dark, grumous, fluid, and acid in reaction; the blood-corpuscles are crenated and do not rapidly form into rouleaux. The body for some time after death retains a high temperature. In early autopsies, necessary in hot climates, the body and viscera when opened feel pungently warm, dark blood drips freely from the incision, rigor mortis comes on rapidly. The brain and membranes are often congested. There may be some cerebral hæmorrhage, effusion of serum into the substance or cavities, or signs of incipient meningitis.

A precise degree of blood-temperature incompatible with life cannot be defined, but the danger becomes very imminent at or above 108° or 109° F.

**Prophylaxis**—Prevention is the great desideratum. The clothing should be very light, and woollen material should always be worn next the skin, as cotton or linen wet with perspiration is very injurious. The head and spine should be protected from the direct rays of the sun out of doors by a pith hat and a cotton pad let into the coat over the back of the neck and spine, and by a good white umbrella lined with green. The clothing should be loose, not constricting the neck or any part of the body. Indoors the temperature should be reduced by the use of therm-antidotes, punkahs, electric fans, or other artificial means of cooling; free ventilation should be insisted on, and a sufficient amount of cubic space—not less than 1000 to 1200 cubic feet per head—in sleeping rooms,

barracks, and so on. During the hot, still nights—a most dangerous time—the foregoing precautions are especially necessary.

Excessive fatigue, excitement, or depression should be alike avoided, though a moderate degree of exercise, physical and mental, is desirable during the cooler hours of the day. A short sleep during the course of the day is also to be encouraged.

For soldiers all drills not absolutely necessary should be avoided. If they must march during the hot weather it should be in the early hours of the morning. Frequent halts should be allowed, and coffee and a biscuit served out. Plenty of water should be carried and be readily available. The dress should be light and loose, and all constriction carefully avoided. The halts should be in the most sheltered places that can be found, with plenty of fresh air—such as open tops of trees. The accoutrements should be as light as possible, so as to spare fatigue and exhaustion. Men falling out should be attended to immediately by the medical officer. Marches and drills in the great heat should be as short as the exigencies of the service will permit.

Moderation of diet is especially to be enjoined. Very little animal food should be taken; the food, whilst sufficiently nutritious, should be light and unstimulating. Iced water should be drunk freely and frequently, and the greatest moderation in the use of stimulants should be observed. Excesses in eating, drinking, or smoking are especially to be deprecated. The cold bath may be freely used. In short, regularity and moderation in all things, and careful attention to the state of the bowels, which should never be allowed to be confined, are essential. No one is more likely to suffer from the ill effects of heat than he who has undergone mental or physical exhaustion, or has suffered from intemperance in food or alcoholic drinks. Healthy persons who lead regular lives and observe such precautions will tolerate a degree of heat which would hardly be deemed credible.

**Treatment.**—In simple heat-exhaustion, remove the patient to a cool place in the shade or into the open air, according to circumstances. Remove all oppressive or tight clothing. Dash cold water on the head and chest so as to rouse but not depress. If necessary, give a stimulant and apply ammonia to the nostrils. If depression continue, administer stimulants and restoratives; let the patient avoid exertion or exposure to heat as much as possible. In the steamers in the Red Sea and Indian Ocean stokers, usually Africans, are sometimes brought up from the furnaces unconscious from heat-exhaustion, but are generally quickly restored by the fresh air, by dashing cold water on their bodies, or by giving a little stimulant.

If a man be struck down by the heating of the hot sun on his head, apply the cold douche freely to the head; if there be rise of temperature, apply ice to the head, but not for too long a time. The object is twofold, to rouse by reflex action and to reduce temperature.

At the capture of Rangoon in 1852, numbers of men under my observation were struck down by the sun, some simply from heat-exhaustion.



They were clad in the thick red coats and leather stocks worn in India in those days. In others, apparently, the exhaustion was combined with the direct effects of the sun upon the head and spine. They were all doused with cold water and placed in the shade in the Field Hospital. All but two recovered; these two were bled on the field where they fell, and never regained consciousness. By recovery is meant a favourable reaction at the time; in some there were consecutive symptoms of fever and cerebral disturbance; they were sent away to a *Depôt* hospital, and if their history could be traced, it would probably be found that in some of them complete recovery never took place. Exposure to the sun's rays should be carefully guarded against, and unless recovery be rapid and complete, a colder climate should be sought, where the same precautions must be continued.

In thermic fever or insolation the object is to reduce the temperature before more serious or fatal consequences appear. For this purpose quinine in doses of 5 grains, or even more up to 10 grains of hydrochloride or sulphate, may be given in solution by the mouth, every three hours; or the equivalent in the form of a hypodermic injection may be given and continued until an impression is produced. Morphine has also been suggested, but this practice seems questionable. Bleeding should not be resorted to except in special cases. In asphyxia, where the right heart is overloaded, it may be expedient as a choice of evils. As a general rule it has been abandoned, for although it may have appeared at first to produce a favourable impression, subsequent results have not justified it as a general practice. No absolute canon of procedure can be laid down with reference to bleeding in this disease; each case must be dealt with on its own merits. All that can be said here is that it is not desirable as a general rule. Should the quinine not be effective in reducing the temperature, antipyrin, phenacetin, antifebrin, aconite, or acetate of ammonia may be tried.

The cold bath, cold affusions, and application of ice to the head—which should be shaved—and to the body, should also be resorted to, care being taken not to prolong the cooling until too great depression be produced—that is, not below 100° F. The bowels should be relieved by calomel, colocynth, and saline purgatives, and by enemas; care being taken that sufficient daily action be maintained. In the epileptiform convulsions which sometimes occur the cautious inhalation of chloroform may be resorted to. I have seen good results from its use. Blisters are sometimes applied to the nape of the neck, but it seems doubtful whether, in the early stages at any rate, they can be of much use, if any. Light and unstimulating diet should be given in small quantities at tolerably frequent intervals. This antipyretic treatment must be continued as long as a high temperature lasts, to obviate the imminent risk of death or of tissue-changes which may be permanently injurious. As the case proceeds, if symptoms of cerebral or meningeal mischief supervene, iodide and bromide of potassium and counter-irritation may be of service.

It is essential that perfect rest of mind and body should be main-

tained. When insomnia is distressing, hypnotics may be useful; they must be given with great caution, and without opium if it can be avoided. Restriction should be imposed upon the use of alcoholic stimulants. The amount, if any, that may be given must depend upon the previous habits as well as the present condition of the patient. Here, again, the physician must be guided by the special indications of the case before him. Precautions should be continued, not only when recovery has set in, but even for some time after it is apparently complete; for certain indications of latent chronic mischief will probably remain, such as loss of memory, irritability, headache, inability to concentrate the thoughts, intolerance of heat, or of the slightest exposure to the sun or even of the temperature of an overheated room. Not until these have completely disappeared can a return to India or any other hot climate be permitted with any propriety or prospect of future health. I repeat that frequently, indeed, a patient can never return to a hot climate at all.

It seems hardly necessary to say that cases of this kind should be removed from a hot climate to a colder one as soon as travelling can safely be permitted, and that the sufferers should be carefully watched on their way home. Neglect of this precaution has resulted in self-destruction during the mental aberration that sometimes follows.

The sequels of sunstroke occasionally assume a serious character, and are the cause of permanent disability to the patient and a source of much anxiety to his friends. The slighter forms of meningitis and of cerebral mischief not unfrequently pass away after protracted residence in a temperate climate, but they are also not unfrequently permanent, and endanger or shorten life, causing such physical or mental disability as epilepsy, partial paralysis, mania, chronic dementia, impaired memory, and inability for mental concentration—sad examples of the evil effects of a tropical or hot climate.

Treatment will depend upon the nature and extent of such mischief. These vary so much as to render it impossible to give more definite directions here, and the reader is referred to the special articles in this System on Cerebrospinal and Mental Diseases.

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## SNAKE-POISON AND SNAKE-BITE

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VENOMOUS snakes are found almost all over the temperate and tropical regions of the world, with the exception of New Zealand and the Oceanic Islands. They are divided by naturalists into two main classes—(i.) poisonous colubrine snakes; (ii.) viperine snakes. These two classes present differences in structure, and also in the properties and toxic action of their poisons.

**Distribution of Poisonous Snakes.**—The following is a list of the better-known and more dangerous poisonous snakes arranged according to their geographical distribution.<sup>1</sup>

**Europe.**—Small vipers or adders (*Vipera berus*, *V. aspis*, *V. ammodytes*) are found on the continent of Europe, and *V. berus* occurs in England. These small reptiles, which are very plentiful in some parts of Europe (e.g. Haute Saône in France), are on account of their small size seldom dangerous to man; but the bite of one is followed by severe symptoms, and according to Bottinger, who collected 610 cases of viper-bite, 10 per cent were fatal. Most of the fatal cases were probably in children.

**India, China, and Southern Asia.**—In Asia are found the most deadly of the poisonous colubrine snakes, the cobra, *Naja tripudians*, and the amadryas or king cobra, *Naja bungarus*, and the kraits, *Bungaruseruleus* and *B. fasciatus*. There are also several species of viper, among which the daboia, *V. russellii*, and the phoorsa, *Echis carinata*, are the most deadly.

**America.**—The important poisonous snakes of the American continent all belong to the Viperidæ, and are representatives of the sub-family Crotalinæ. In North America are various species of rattlesnake, *Crotalus terrificus*, *C. scutulatus*, *C. durissus* and *C. horridus*, and the copperhead *Ancistrodon contortrix*, and the moccasin, *A. piscivorus*. In South America a number of different species of the genus *Lachesis* (*L. mutus*, *L. lanceolatus*, *L. atrox*) are found, many of which reach a size of four or five feet or even more. Of these the Fer de lance, *L. lanceolatus*, is perhaps the best known. *Crotalus terrificus* also occurs in Brazil and Northern Argentina.

**Africa.**—In the North of Africa a species of cobra, *Naja haje*, is common; and two vipers, *Cerastes cornutus* and *Echis carinata*, are responsible for a number of deaths.

In the South are found another species of cobra, *Naja flava*, and two vipers, *Causus rhombeatus* and *Bitis arietans* the puff-adder.

In Australia and Tasmania are a large number of species of venomous

<sup>1</sup> The nomenclature adopted in this article is that given by Mr. Boulenger in his *Catalogue of Snakes*, British Museum of Natural History, vol. iii., 1896, to whom we are indebted for assistance with regard to the distribution of snakes.

snakes, all of which belong to the Colubridæ, although the death-adder, *Acanthophis antarcticus*, simulates a viper by its appearance. The principal species dangerous to man are *Notechis scutatus*, the tiger snake; *Dendrodon superba*, the copperhead; *Acanthophis antarcticus*, the death adder; *Therapsia tertiis*, the brown snake, and *Notechis pseudon*, the black snake.

*Sea Snakes.* The Hydrophinae are all poisonous. With the exception of *Platurus* they live entirely in the water, their tails being flattened like that of an eel. They are common in the tropical and subtropical seas of the Indian and Pacific Oceans.

**Poison Apparatus and Mechanism of Bite** The poison is secreted by the cells of a racemose gland, possessing large alveoli which serve as a receptacle for the venom. The glands, one on each side of the head, are placed behind the orbit. In an adult cobra they are about the size of a large almond. The gland is the homologue of the parotid salivary gland in other vertebrates. They are subcutaneous, with no exception of the superior portion of their external surface. Each is enveloped in a dense capsule of fibrous tissue, from which two strong fascial processes extend anteriorly and posteriorly, so as to fix it securely both in front and behind. The gland is in intimate relation with the masseter muscle, which consists of two portions, the superior portion arises from the external surface of the post-orbital bone, the edge of the parietal, and the crest of the exoccipital, and is inserted into the external surface of the gland capsule, the inferior portion arises as a flat tendon from the upper part of the posterior half of the internal surface of the gland, and passes downwards deep to the gland, to be inserted into the mandible and dentary. When the snake bites, the gland is, owing to the peculiar insertion of the masseter powerfully wrung, and the poison expressed into the duct, much in the same way as one expresses moisture from the pores of a cloth by twisting it. That the muscle does indeed act in this way can be seen if the recently severed head by stimulating its nerve with a faradic current. A large lymph space surrounds the gland and so permits of this twisting. From the anterior margin of the gland the duct passes forward over the side of the upper jaw. Just in front of the fang it doubles on itself so as to open by a small papilla on the anterior wall of the sheath of mucous membrane which embraces the base of the tooth. The gland duct is composed of fibrous tissue, and is lined with epithelium. Numerous small gland alveoli open along its course. Wen Mitchell found a muscular sphincter in the course of the duct in *Crotalus*, but in other species no muscular tissue has been observed.

The fang, except in some of the sea snakes, is a functional tube with the proximal opening on the anterior surface near the base and the distal opening on the same surface within a short distance of the point. In the centre is a pulp cavity containing vessels and nerves. During the development of the poison-fang it first becomes flattened anteriorly, ridges then arise on the anterior surface, which, as a

quent folding of the whole tooth, are brought into contact and sealed. Thus there are now two cavities in the fang, a round poison cavity and a horse-shoe-shaped pulp cavity. This folding over is incomplete near the base and point of the tooth. In ordinary circumstances the fangs project downwards and more or less backwards, and are almost completely covered up by a sheath of mucous membrane (*vagina dentis*).

When the animal is about to strike they become erect. Different snakes vary very greatly as regards the angle through which they can swing the maxillary bone and with it the poison-fang. Snakes in which long fangs are found (*Viperidæ*) can do this to a very considerable extent; in the colubrines this movement is relatively insignificant.

The upper jaw is formed of the pterygoid behind, and in front by the alveolar bars which diverge at a slight angle. The internal of these bars is the pterygoid, the external the transverse with the maxilla in front, to which at last the poison-fang is attached.

The maxilla is fixed anteriorly to the convex inferior surface of the pterygoid by a joint which permits of a certain amount of gliding, and the anterior surface of the pterygoid is connected by a ligament to the sphenomandibular joint. The whole bar is freely movable in an antero-posterior direction. When the pterygo-transverse bar is moved forwards, the maxilla is pushed forward. The forward movement of the maxilla is, however, soon stopped by a strong ligament attaching it to the præ-frontal. If now the pterygoid and transverse advance forwards, bending occurs at the joint between the transverse and the maxilla, the latter rotates with its lacrimal attachment as a fixed point, and the fang presents in a still more forward direction. The pulling forwards of the pterygoid bar is in all cases performed by the sphenomandibular and parieto-ptyerygoid muscles.

Except when the snake is prepared to strike, the poison-channel from the gland-duct to the fang is not completed. As already mentioned, the duct opens on a papilla, which is situated on the anterior surface of the sheath of mucous membrane which embraces the fang (*vagina dentis*). To complete the channel it is necessary that this papilla be brought into apposition with the opening of the poison-canal at the tip of the fang. This apposition of the orifice of the poison-duct with the opening in the fang is brought about with wonderful exactness, and in our experience we can only recollect two instances in which the union at this point was leaky. It is accomplished in Australian snakes partly by the pulling forward of the anterior surface of the fang to the opening of the duct, in the erection of the former as described above, and partly by pulling the mucous sheath backwards tightly against the tooth. This latter is accomplished precisely at the right moment, when one of the most important muscles in closing the jaws upon any prey is contracted.

When bitten, the internal pterygoid, sends off two small tendinous processes which are inserted into this mucous sheath on each side of the opening, so that the harder the reptile bites the tighter the papilla is closed.

pulled into the proximal aperture of the fang canal. The aperture is by this means actually corked. When the snake strikes it closes its jaw like a dog on the part bitten. Thus the poison is discharged at the moment the fangs penetrate the skin.

**The Effects of various Reagents on the Toxic Properties of Venoms.**—Reagents which precipitate proteids in an insoluble form, or destroy them—such as platinum or gold chloride, silver nitrate, nitric acid in excess, or permanganate of potash,—render venoms inert. Solutions of the hypochlorites have the same effect. Carbolic acid if allowed to remain in contact with dilute venom for twenty-four hours destroys its virulence. Prolonged action (forty-eight hours) of caustic potash or soda also destroys venoms. Gastric digestion does not affect cobra-venom nor pseudoechis-venom. Weir Mitchell states that gastric digestion destroys the power of crotalus-venom. Fontana found the poison of the European viper to be unaffected by this means. All venoms are destroyed by pancreatic digestion.

Under a variety of conditions the toxins of venoms undergo change whereby their toxicity is diminished or lost, whereas the power of combining with the corresponding antitoxin is maintained (toxoid formation). This was first pointed out by Drs. Myers and Stephen Flexner and Noguchi have made some most interesting experiments on the formation of toxoids from the natural venoms. Working with the venoms of the cobra and of the rattlesnake, they found that the neurotoxin was converted into toxoid by keeping a sterile solution of the poison for some time at room-temperature; this change took place more rapidly when the solution was kept at  $37^{\circ}$  C. The hæmolysin also undergoes rapid toxoid formation when the venom solution is kept at  $37^{\circ}$  C. Such treatment has, however, no effect on the hæmorrhagin, the constituent of crotalus-venom which is responsible for the severe local reaction and for the hæmorrhages, and which these observers consider to be of the nature of a cytotoxin for the endothelium of the capillary and arteriole walls. If, however, crotalus-poison be treated with hydrochloric acid in weak solution, namely 0.2 to 1 per cent, there is a marked diminution of activity of the hæmorrhagin constituent; this diminution is of the nature of a toxoid formation, since by injecting rabbits with a venom solution heated in this way a fairly strong anti-hæmorrhagin serum could be prepared. Similarly by treating crotalus-venom with a solution of iodine trichloride (0.2 per cent) toxoid formation of the hæmorrhagin was obtained. Cobra and daboia poisons treated in the same way with iodine trichloride failed entirely to yield any toxoids, the poisons being completely destroyed.

**Separation of the Poisonous Constituents of a Venom.**—The different toxins, a mixture of which constitutes a particular venom, have in some cases been separated from one another. This has been accomplished in several ways.

(1) Heating to  $70^{\circ}$  to  $100^{\circ}$  C., according to the particular venom. Fibrin-ferments, hæmorrhagins, and some neurotoxins are destroyed at



75°-80°, whereas other neurotoxins and some hæmolysins, *e.g.* cobra, withstand boiling.

(2) Dialysis or filtering through a gelatin filter supported in the pores of a Pasteur-Chamberland candle, *e.g.* fibrin-ferments and hæmorrhagins do not dialyse.

(3) The hæmolysins may be separated from neurotoxins and the other cytolytins by digestion with red blood-cells in the presence of serum previously heated to 56° C.; and the cytolytins for any given organic cell of an animal may be abstracted from a venom by digesting it at 0° C. with an emulsion of such cells. In the same way it has been found that the neurotoxin is absorbed by brain-cells (Flexner and Noguchi).

(4) The hæmolysin of cobra-poison can be separated from the neurotoxin by shaking a solution of venom with lecithin dissolved in chloroform. The hæmolysin combines with the lecithin to form an active lecithide, which dissolves in the chloroform and can be subsequently precipitated by ether; the neurotoxin remains in the watery solution. The cobra lecithide is strongly hæmolytic for the red cells of all species with which it has been tried. Its action is very rapid; in concentrated solution almost instantaneous. It is not damaged by heating at 100° C. for six hours, and is much less influenced by a cobra-venom anti-serum than the hæmolysin of the original poison.

The watery portion separated out by centrifuging contains the neurotoxic constituent of the venom quite free from hæmolysin. Jacoby has immunised a rabbit with this neurotoxin and has obtained a serum which has a weak neutralising action on the neurotoxin of the original venom. Working in the same way with several other venoms, Kyes has been able to prepare hæmolytic lecithides; that is to say, compounds of lecithin with the hæmolytic constituent of the venom.

**The Toxic Value of Venoms.**—Different venoms vary greatly as regards their degree of toxicity: also the minimum lethal dose of any given poison varies somewhat for different animals weight for weight.

Sir T. R. Fraser and Major Elliot found that if the minimal lethal dose of cobra-venom per kilogramme of body-weight for rats be taken as unity, that for rabbits = 1·2 and that for cats = 20, whereas the minimal lethal dose of the venom of a sea-snake, *Enhydrina valakadien*, the action of which is very similar to that of cobra-poison, shewed a totally different relationship for the same three animals. In this case the lethal dose was less per 100 grammes for rabbits than for rats, and if the minimum for rabbits were expressed as unity that for rats was 1·5 and for cats 3·3. Sir T. R. Fraser and Major Elliot regard these results as indicating a material difference in the constitution of the two venoms, notwithstanding the similarity of their physiological action. The following table shews the minimum lethal dose of some of the more important poisons for the rabbit expressed in milligrammes per kilogramme of weight. In making such comparisons it is important that only venoms derived from recently captured snakes be employed; for in confinement, not-

withstanding forced feeding, their poison soon shows a falling off not only in total amount and in concentration but also in the toxicity of the dried residue. On this account the figures in the table below must be regarded as approximate only.

Species of Snake	By Subcutaneous Injection.	By Intravenous Injection.
India— <i>Naja tripudians</i>	0.35 milligrammes	
<i>Naja bungarus</i>	0.35 "	
<i>Bungarus ceruleus</i>	0.08 "	0.04 milligrammes
<i>Bungarus fasciatus</i>	2.5–3 "	0.7
<i>Echydria valakadien</i>	0.05 "	
Australia— <i>Notechis scutatus</i>	0.05 "	
<i>Damenia textilis</i>	0.2 "	
<i>Acanthophis antarcticus</i>	0.2 "	
<i>Notechis pseudochis</i>	0.6 "	
India— <i>Daboia russellii</i>	1–2 "	0.1 milligrammes
<i>Echis carinata</i>	1–2 "	0.05
<i>Lachesis gramineus</i>	"	2
America— <i>Crotalus durissus</i>	"	0.25

The most toxic venoms are evidently those of the Australian tiger snake and the sea snake, *Echydria valakadien*, then comes that of the krat, *B. ceruleus*. The least toxic are those of the banded krat and the green pit viper.

**Description of Venoms.**—To obtain venom in a pure state for purposes of chemical examination and experimental inquiry, the best method is to allow the snake to bite an ordinary large watch glass which has been covered with thin rubber sheeting, such as dentists use. The fangs penetrate the rubber and all contamination by the secretions of the mouth is effectually prevented. Collected in this way the amount of dried venom which a recently captured adult cobra yields varies from 600 to 1,100 c.c. containing 200 to 370 milligrammes of solid matter, a large daboia yields about the same quantity of liquid venom, namely, from 6 to 1 c.c., but containing less solid matter—150 to 250 milligrammes; the quantity of poison obtained from the smaller Indian snakes, such as the krat and the phooras, is very much less. Calmette obtained the following yields of poison from snakes in captivity:—

Variety of Snake	Weight in Milligrammes, as discharged.	Weight in Milligrammes dried.
Lacerta (medium size)	320	127
Crotalus (large)	370	105
Cerastes	123	27

One of us (C. J. M.) found the maximum yield of two species of Australian snakes to be

	Weight in Milligrammes, as discharged.	Weight in Milligrammes, dried.
Australian tiger snake ( <i>Notechis scutatus</i> )	205	73
Australian black snake ( <i>Notechis pseudochis</i> )	160	94

If a snake be kept for some time in captivity and the poison extracted regularly, the amount of venom that can be obtained by this method is considerably diminished, so that after some months' incarceration perhaps only thirty or forty milligrammes can be got from a full-sized cobra.

Snake-poison is in most instances a clear limpid fluid of a pale straw yellow colour. Some venoms, however, such as that of *Echis carinata*, are always a certain amount of suspended matter. The colour varies with the degree of pigmentation of the snake, and also with the concentration of the venom. The reaction of the venom is almost invariably acid. The alkalinity observed in some cases may be accounted for by admixture with alkaline saliva. The specific gravity of venoms varies considerably; the average of the poison obtained from 250 cobras was 1.110, while the average of the venom from 53 daboias was found to be 1.077 (Lamb). The amount of solids contained in these two poisons was found to correspond with the specific gravity; thus, the percentage of solids in cobra-venom was on an average 31.5 and in daboia-venom 24.4. The variations, however, are considerable, in the case of cobra-venom being from 23 to 35 per cent. Most venoms are tasteless, but cobra-poison has a disagreeable, intensely bitter taste.

Venoms dry rapidly at 16° to 20° C. in a desiccator over calcium chloride. As they dry they crack in the same manner as albumin or dextrin in the same circumstances, and form translucent scales which suggest a crystalline structure. Dried venoms dissolve again easily and completely in water. Perfectly dry venom in a well-corked bottle keeps indefinitely. Weir Mitchell kept some crotalus-venom in his possession twenty-two years without apparent diminution of toxic power.

We have had some venoms for thirteen years which are as deadly at the present time as when first procured. Venoms in solution in water do not putrefy; and the numerous assertions that dried venom deteriorates with age may be accounted for by imperfect desiccation. Solutions of venom in glycerin keep indefinitely (Weir Mitchell).

Microscopical examination of pure venom reveals nothing except an occasional epithelial cell; but if the poison be contaminated with fluids from the mouth it contains epithelial scales and salivary corpuscles in abundance, and also bacteria of various kinds.

*Composition of Venoms.*—It has long been known that snake-venoms contain albuminous bodies in solution; but, owing to ignorance of the chemical properties of proteids, the active principle was sought for in other constituents. Weir Mitchell was the first to demonstrate that the

poisonous properties of rattlesnake-venom reside in the albuminous constituents; and the work of this accomplished author on the venom of the rattlesnakes formed the first step in our knowledge of toxic proteids. Since Weir Mitchell's work was published his results have been extended by other observers to a number of different kinds of snakes.

Venoms consist for the most part of solutions of modified proteids, and all attempts to separate the toxic principles from such proteids, a separation which has, for example, been accomplished by Jacoby and Hausmann for ricin and abrin, have hitherto been unsuccessful. Accordingly, at the present time we must regard such toxic principles as residing in some special grouping of a portion of the atoms in the complex venom proteid molecule; although it is possible that this is a side-chain and may be ultimately capable of differentiation as a separate entity. Venoms are by no means simple solutions of one poisonous substance; the more they have been studied the more complex have they been shewn to be. The analysis of their physiological actions has proved them to be made up of a great many more constituents than would be imagined from their chemical examination. Different venoms have been found to contain one or more of the following:—(1) A powerful fibrin-ferment; (2) an anti-fibrin-ferment; (3) a proteolytic ferment; (4) various cytolsins—capable of acting upon red blood-cells, leucocytes, endothelial cells of vessels, nerve-cells, and the cells of various other tissues; these cytolsins are probably distinct for each variety of cell and are of the nature of amboceptors; (5) agglutinin for red blood-cells, etc.; (6) an antibactericidal body, of the nature of anti-complements; (7) a neurotoxin or neurotoxins with affinities for all nerve-cells and especially for the cells of the respiratory centre in the bulb, although the special affinities of the neurotoxic constituents vary somewhat with each venom; (8) a neurotoxin with an affinity for nerve-endings in muscle, and for those in the diaphragm in particular; (9) a substance which causes greatly increased tone in cardiac muscle, and if in sufficient concentration systolic standstill of the isolated heart. This substance produces also a similar stimulating action on the muscle of the arterial walls. No venom yet studied is possessed of all the above constituents, and the dissimilarity in the effects produced upon man and animals after poisoning with the venoms of different snakes is due to the proportions in which the different groups of toxic substances occur in the particular venom. While in different venoms we may recognise substances with the same physiological action, it is not to be taken for granted that such substances are identical. Recent experiments with the serum of animals immunised with different venoms have shewn that many of these constituents from different venoms, even when incapable of differentiation by their physiological action, display their non-identity by the inability of an anti-serum prepared with one poison to neutralise the constituents of similar action of another poison; or expressed in terms of Ehrlich's nomenclature, that, although the toxophorous groups may be similar, the haptophors are dissimilar. This has been especially shewn in the case of the hæmolysins of venoms.

Further, by means of the serum precipitin test it has been shewn that the proteids of one venom may differ from those of another poison, although the physiological actions of the two venoms are apparently identical. Thus, the serum of a rabbit immunised with pure cobra-venom causes a copious precipitum with cobra-venom, but none whatever when mixed with the venom of the king cobra, the physiological action of which poison cannot be differentiated experimentally from that of the cobra. The importance of these facts on the specificity of venoms in connexion with the serum therapeutics of snake-bite will be at once evident, and we shall have to return to this question later when discussing the treatment of cases of snake-venom intoxication.

*Behaviour of Venoms with Reagents.*—Venoms give all the reactions characteristic of proteids with the usual proteid-reagents. On dialysis more or less of the proteid in venom is thrown out of solution, the amount varying with different venoms. To judge by the hitherto recorded observations, it is greatest with crotalus-poison, and least with that of the cobra. Saturation with ammonium sulphate completely precipitates all the proteids, and the filtrate is innocuous. Saturation with sulphate of magnesium, or chloride of sodium, and partial saturation with ammonium sulphate produce a separation of the proteids in venoms, and in the case of most venoms both the precipitate and the filtrate are possessed of poisonous properties. Absolute alcohol *in excess* entirely precipitates all proteids from venom solutions, and the filtrate is not poisonous. After sojourn under alcohol the bulk, and in some cases the whole, of the proteid is readily soluble in dilute saline solutions, and the solution possesses the same properties and nearly the same toxicity as the original venom.

*Effect of Heat upon Venoms.* Solutions of all snake poisons so far examined contain a considerable amount of proteid coagulable by heat, which, according to the observations recorded below, appears not to vary greatly in the poisons of different species of snakes. The following table gives the percentage for the venoms of three Indian species—two colubrine and one viperine—and of crotalus:—

	Cobra	Banded krait.	Daboia.	Crotalus.
Coagulable proteids .	24	20	25	25
Non coagulable proteids	76	80	75	75
Temperature at which coagulation takes place	70-80 °C		70-80 °C	60°-70 °C

Although the amount of proteid coagulated by heating varies so little, the effect produced upon the toxicity of the different venoms by bringing their solutions to a temperature of 70-80 °C. for a few minutes is strikingly different. Cobra poison, for instance, is little if at all reduced in toxicity by such treatment; whereas the venoms of the viperine snakes, crotalus and daboia, are rendered nearly but not quite inert. The effect upon a number of other venoms, such as those of the Australian snakes, *Notechis*

*scutatus* and *N. pseudechis*, is intermediate ; they lose some portion of their toxic qualities whilst retaining others. When a particular coagulable constituent is toxic, raising the solution to the temperature at which this coagulates renders it inert. If the heating be carried to the boiling-point a further gradual diminution in toxicity is brought about in all venoms, and continuous boiling for a few hours deprives them of all poisonous action.

The effect of heat is twofold :—(1) a more or less rapid destruction of a poisonous constituent of some venoms by coagulation ; (2) a gradual deterioration by prolonged heating, the effect of which is more rapid the higher the temperature and the weaker the solution.

Perfectly dry venoms may be submitted to a temperature slightly above 100° C. without diminishing their toxic power. Some of the proteids present in venoms are classified with difficulty in our present system. A classification which is determined (amongst other reactions) by solubility in water or dilute saline solutions, coagulation by heat, and solubility or insolubility in water or saline solutions after prolonged sojourn under alcohol, is a very arbitrary one ; and it is to be expected that, as our knowledge of proteids increases, more individuals of the group will be found which refuse to fall into line with the members hitherto known. The toxic proteids of the poison of *pseudechis* are completely precipitated by absolute alcohol in excess ; yet after six months under alcohol these proteids dissolve readily and entirely in dilute saline solutions. This poison, nevertheless, contains a body which, by its solubility in water and coagulation by heat, would lead one to class it with albumins. The solution of the alcoholic precipitate also coagulates on heating. Venoms contain proteids which possess on the one hand characteristics of the albumins or globulins, and on the other those of proteoses. This has led to a certain amount of confusion—one observer classifying a venom proteid with the albumins or globulins because of its behaviour when heated in solution, another preferring to place the same proteid amongst the albumoses on account of its continued solubility in water or dilute saline solutions after prolonged sojourn under alcohol.

**Analysis of the Physiological Action of Snake-venoms.**—*Method of Absorption of Venom.*—Venoms may enter the body by a number of channels. The onset and train of symptoms vary with the rapidity with which they reach the circulation. In cases of snake-bite the poison is usually deposited in the subcutaneous tissue, whence it reaches the general circulation, principally by absorption through the blood-vessels. When introduced into a serous cavity, absorption is much quicker ; and, if introduced directly into a vein, the effects are manifested instantaneously. Venoms are readily absorbed from the conjunctiva. Feeding an animal with snake-poisons, even when the diet contains daily a hundred times the fatal dose, does not produce any symptoms of poisoning, provided there be no abrasion of the mucous membranes. The poison has not been recovered from the fæces, so that it must be



destroyed by the digestive juices. As mentioned above, pancreatic juice has been found to destroy all those venoms with which the experiment has been made. Major Elliot has shewn that when the actions of the various digestive juices do not come into play cobra-poison can be absorbed from the small intestine. There is a striking difference in the effects produced by subcutaneous and intravenous injection of moderate quantities of those venoms which contain fibrin-ferment (see p. 800). Even very small quantities of such poisons intravenously introduced occasion extensive intravascular clotting and sudden death; whereas, placed under the skin, unless in relatively large quantities, the thrombosis is only local, and this in itself retards the further absorption of the poison.

*General.*—During recent years not only has a considerable amount of experimental work on the physiological action of different snake-venoms and on the individual poisons contained in them been carried out, but great strides have been made in our knowledge of the mode of action of toxins, cytolytins, and enzymes, to which venoms are closely analogous. The poisonous constituents of venoms, as has been previously mentioned, are modified proteids. They belong to the first of the two main groups into which Ehrlich has divided substances possessing pharmacological action. Ehrlich's view of the action of this group is bound up with his conception of the nature of the living protoplasmic molecule as a nucleus with side-chains of various descriptions. According to this hypothesis, assimilation of food-stuffs consists in the linking on to the central molecule of the food-molecule as a fresh side-chain. The common features of substances of this first class are their close resemblance to assimilable substances or food-stuffs, and the special affinity exhibited by different bodies of this class for particular cells. They are thus, so to speak, selectively absorbed by one class of cells from the circulating fluids, so that they gradually become attached to them, and to them only. In this way even excessively small quantities exercise a potent influence.

This first group of Ehrlich includes all those bodies with chemical character more or less allied to proteids, to which the toxins and enzymes belong. All of these, whether produced by the activity of bacteria—as tetanus or diphtheria toxins,—or by higher plants—as ricin, abrin, or the toxin of grass-pollen, which is responsible for hay-fever,—or in animals—as rennet, trypsin, or the venoms of snakes,—are produced by living cells. These toxins and enzymes possess the capacity of attaching themselves to particular cells or molecules, much as a key fits a particular lock or series of locks; and being affixed to the cell they occasion such a disturbance of the normal activities of the cell that its function is disturbed or destroyed, and in some cases the cell itself is disorganised. They also possess in common the capacity of arousing the formation of anti-bodies in excess when injected into an animal at suitably spaced intervals.

For these and other reasons snake-venoms must be classed with toxins, lysins, and enzymes, and a general survey of the principal actions of their constituents shews that they may be grouped in three classes:—

(1) Neurotoxins, which combine with nerve-cells and render them inactive. These often exhibit a strikingly selective action upon particular groups of cells. (2) Cytolysins, for a number of animal cells, such as red blood-corpuscles, endothelial cells of blood-vessels, leucocytes. (3) Fibrin-ferments, the injection of which occasions intravascular clotting. This does not exhaust the whole of the poisonous components of some venoms which contain, in addition to representatives of one or more of the above groups, substances possessed of actions, such as that of cobra-poison on the muscular tissue of the heart and arterial wall, or that of a constituent of rattlesnake-poison which inhibits the normal bacteriolytic action of the serum. There are also proteolytic ferments in crotalus and some other venoms, but these are of subsidiary importance, and along with others will be mentioned later.

Poisons which possess a special affinity for nerve-cells are present in greater or less amount in all venoms, but, speaking generally, they are of greater potency and are present in greater amount in the venoms of colubrine snakes than in those of the Viperidæ.

One or more cytolysins exist in most venoms, and have been shewn by Flexner and Noguchi to be of the nature of amboceptors; after these have combined with the cells the latter undergo destruction and solution under the influence of complements contained in the animal's own serum. Many venoms exert a destructive action upon more than one class of cell, an action brought about by the presence of a plurality of cytolysins (Flexner and Noguchi). The action of some of the best known cytolysins in venoms will be discussed in dealing with that of snake-poisons upon blood and blood-vessels.

The fibrin-ferments exist in greater or less amount in the venoms of viperine and in many of the colubrine snakes. Their action is important in bringing about the rapid death of small animals on which these reptiles prey: but this result seldom occurs in cases of snake-bite in the human subject, unless the poison has accidentally been introduced directly into a vein.

Every venom does not contain toxins belonging to all three of the above groups, and the difference in the results of the injection of the poison of different snakes is largely due to the variation in the proportion in which representatives of the above groups exist in venoms. The constituents of different venoms belonging to the same group are not usually identical, but display differences in the details of their action; and even when this action is similar, the absence of complete identity is shewn by the observation that an anti-body produced against one particular toxin is either without effect upon others or else requires a considerably increased amount to neutralise it.

*Action of Venoms on the Nervous System.* — The determination of the exact physiological action of a poison on the nervous system of the higher animals is always difficult. The difficulties are enormously increased when the poison, as is the case with some snake-venoms, contains constituents which profoundly affect the blood and the whole circulatory

**apparatus** also. In such a case special precautions have to be taken to **distinguish** effects which are due to the primary action of the poison on **nervous tissue** from those which are secondary to changes produced on **the circulation and blood**. The early experimenters did not realise **that** most viperine and many colubrine venoms contain fibrin-ferments, **which** occasion extensive intravascular clotting if introduced directly **into** the blood-stream even in minute quantities, and often do so when **subcutaneously** injected in larger amounts into small animals; this **has** naturally been the cause of the greatest confusion in interpreting **some** of their experimental results, especially those in which the **poison** was introduced into a vein. The striking manifestations of **disturbance** of nervous activity which follow sudden cessation of the **circulation** have, in ignorance of this property of some venoms, been **attributed** to the direct action of the poison upon the nervous system.

The general feature of poisoning by all venoms consists in depression of nervous activity, with gradual onset of inco-ordination, lethargy with **diminished** reflex response, coma, and cessation of respiration. The **particular** feature of the poisoning by individual snakes is determined **by** the potency and character of the neurotoxin contained in its venom, **and** the relation of this neurotoxin to constituents toxic for other cells of **the organism**.

The venoms of colubrine snakes, the physiological action of which has **been** studied in some detail, are those of the cobra, hamadryas, the kraits, **the sea-snake**, *Enhydrina valakadien*, the Australian snakes, *Notechis scutatus*, *N. pseudechis*, and *Acanthophis antarcticus*. With all of these venoms the **paralytic** action upon the nervous system is the best marked feature of **their** action. Frogs injected with these poisons soon lose all reflex **activity**, and their spinal cords become totally inexcitable. Mammals **become** progressively paralysed until death ensues from paralysis of the **respiration**; if, as is the case in cobra-poisoning, the circulation be well **maintained**, the animal may be kept alive by artificial respiration for **hours**, during which period reflex action is entirely abolished. Cobra-**venom** is particularly suitable for this experiment, as owing to the direct **stimulative** action of this venom upon the arterioles the blood-pressure **does** not fall.

Respiratory paralysis is quickly brought about in mammals by **bringing** the poisons into contact with the central nervous mechanism **which** controls respiration; this can be done by placing a few drops of a **solution** of venom in the fourth ventricle.

If, after the subcutaneous injection of one of the above venoms, **simultaneous** records of the respiration and blood-pressure be taken **during** the poisoning of a dog or rabbit, the circulation is found to be **fairly** well maintained up to the time that all respiratory movements **have** ceased, and may subsequently undergo a marked asphyxial rise, **showing** that the vasomotor centre is still functionally active. If, **however**, asphyxia be obviated by artificial respiration, the vasomotor centre **fails** shortly after the respiratory centre, and the pressure slowly falls to

a few millimetres of mercury pressure, except in experiments with cobra-poison and that of *Bungarus caeruleus*, where direct arterial constriction occurs.

From what has just been said it is clear that certain groups of nerve-cells in the medulla exhibit a special susceptibility to the action of the neurotoxins in these venoms, and that the cells connected with the central nervous mechanism of respiration are particularly affected. The neighbouring cells in the bulb participate early in the paralysis, so that more than one observer has drawn attention to the similarity of the symptoms of snake-poisoning to those of the late stages of bulbar paralysis.

The influence of the neurotoxins of venoms upon nerve-cells is not confined to an interference with function; in cases where they have been looked for, structural changes in the nerve-cells have been found to follow injections of these poisons. Kilvington found that the cells of the spinal cords of rabbits poisoned with the venom of *Notechis scutatus* exhibited degenerative changes resembling those described by Dr. Mott in abrin-poisoning. Preparations stained by Nissl's method shewed chromatolysis and ultimately disappearance of all staining particles. No swelling of the cell occurred; the nuclear outline vanished, and in some cases disappeared, but the nucleolus remained. Many of the cells were represented by mere "ghosts," which suggested a cytolytic process. Unless the animals survived the poisoning for four or five hours no changes in nerve-cells could be detected.

The nervous systems of monkeys killed with the venom of cobra, of *Bungarus fasciatus*, of *Bungarus caeruleus*, and of daboia, have been examined microscopically by Lamb and Hunter. With the venoms of the first four they produced an acute chromatolysis of the ganglion-cells throughout practically the whole cerebrospinal nervous system. These changes were, as a rule, most marked in the cord, less so in the cerebral cortex, and least apparent in the pons and medulla; the longer the animal lived after receiving the venom the more extreme was the chromatolysis. No changes were visible in the ganglion-cells of monkeys dying within two hours of injection. In none of the animals did the peripheral nerves shew signs of degeneration. No changes in the nerve-cells were observed in monkeys killed with the poison of *Daboia russellii*, although one of them lived for sixty hours. It has already been mentioned that venoms contain cytotoxins for red blood-cells, leucocytes, endothelium, etc. In the case of these cytotoxins the mechanism has been shewn by Flexner and Noguchi to be analogous to serum-hæmolysis, the venom constituent acting as an amboceptor, and the cell destruction being brought about by a complement present in the animal's own serum. The appearances seen in the nerve-cells of animals which have lived for two or three days after snake-poisoning strongly suggest that the action of the neurotoxins may also belong to this category. This view would explain both the latent period which ensues before the onset of paralysis, when only minimal fatal doses are employed, and also why no changes

can be detected in the cases in which death ensues within a few hours.

With viperine poisoning direct action upon the nervous system is not nearly so marked as with the venoms of the colubrines. The neurotoxins of viperine venoms are less potent, or present in much smaller amount, while the actions of the other constituents in these poisons are more pronounced.

Of the poisons of the viperine snakes, those of *Crotalus*, *Daboia russellii*, and *Lachesis anomala* have been best studied with regard to their action upon the nervous system. Symptoms of general depression of all nervous activity occur under the influence of these poisons, but the respiratory nervous mechanism does not appear to be selectively affected. As will be mentioned later, these poisons occasion a striking fall of blood-pressure, which is due to an action upon the vasomotor mechanism, and is attributed by Major Rogers to paralysis of the central mechanism. Simultaneously with the fall of pressure the respiration becomes shallower and slower until it ceases.

There exist also in some venoms, e.g. those of the cobra (Brunton and Fayrer), king cobra, kraits (Rogers), *Enhydryna valakadien* (Fraser and Elliot), neurotoxins which act upon the nerve-endings in voluntary muscle or on the neuro-muscular junctions, in a manner analogous to the alkaloid of curara. This action is more easily made evident in experiments in which the poison takes some hours to kill, or in those in which death from central respiratory failure has been obviated by artificial respiration. The phrenic nerve-endings appear to be particularly susceptible to this action, for it is found that the diaphragm ceases to respond to the stimulation of the phrenic nerves at a time when irritation of the brachial or sciatic plexus with the induced current produces good contractions of the corresponding muscles. This curara-like action is not always present in venoms which kill by causing cessation of respiration. The poisons of the Australian snakes, *Notechis scutatus* and *N. pseudochis*, both of which contain powerful neurotoxins with a special affinity for the respiratory centre, have no such action, nor was Feoktistow able to discover any such action with the venoms of *Crotalus* or *V. berus*.

*Chronic Intoxication due to Action upon the Nervous System.*—The poison of the banded krait *Bungarus fasciatus* contains a neurotoxin which possesses an action not observed in poisoning by other snakes. Wall first pointed out that in acute poisoning by this venom the symptoms resembled those of cobra intoxication, and death took place from paralysis of respiration; if, however, a small quantity of poison was injected, the animal shewed no acute symptoms, but after a few days, in which no departure from health was noticed, suffered from a chronic wasting illness characterised by loss of appetite, great depression, irregular temperature, and excessive muscular weakness. Purulent discharges took place from the eyes and nose, and albumin was found in the urine. The muscles became more and more atrophied, and the increasing weakness passed into a condition of general paralysis and death. Dr. W. Hunter and one



of us (G. L.) examined the nervous systems of monkeys which succumbed in about ten days to this chronic intoxication, and found extensive primary degeneration of most of the nerve-cells in the brain and cord. The majority of the cells were vacuolated with deeply stained plasma, in which were scattered dust-like granules, the remnants of the Nissl-bodies. Many of the cells were reduced to simple outlines without any granulation whatever.

*Effect of Venoms upon the Respiration.*—The selective activity of the venoms of colubrine snakes upon the respiratory cells in the medulla, which have hitherto been the subject of inquiry, has been already mentioned. It has further been pointed out that some venoms also exert a curara-like action which is particularly manifested upon the nerve-endings of the phrenics in the diaphragm, so that failure of respiration, brought about in one or both ways, is the cause of death in poisoning by the venoms mentioned.

Perhaps one of the most striking demonstrations of this action was the early experiment of Sir Lauder Brunton and Sir J. Fayerer on the fowl. If cobra-venom be injected into a fowl, the creature becomes lethargic and inco-ordinate; the head drops on the breast, to be occasionally jerked up again, as happens with a man sleeping in a chair. Presently the respiration, which was at first accelerated, becomes slower and more and more shallow, until it finally ceases: meantime the comb has become livid. If artificial respiration be performed, the comb again recovers its bright red colour, again to become livid on its cessation. This may be repeated a dozen times. The obvious interpretation of this experiment is that in cobra-poisoning the respiratory movements are rendered impossible whilst the circulation is well maintained. The same facts are seen when mammals are the subject of experiment; after a preliminary increase in respiratory activity, a progressive diminution in number and amplitude occurs, until respiration ceases altogether. Small animals poisoned with cobra-venom have been kept alive for four hours by artificial respiration; and Vincent Richards records a case in which the circulation was maintained, by means of artificial respiration, for thirty hours in a man poisoned by a cobra. This selective action of a poison for the respiratory mechanism is seen in a most marked degree with the poisons of the cobras and the sea-snake, *Enhydrina culakadia*. With the other colubrine venoms the vasomotor mechanism becomes affected shortly after the respiratory, so that the blood-pressure falls and circulatory failure follows respiratory failure within a few minutes or an hour, according to the conditions of the experiment and the venom employed. The respiratory movements are, as mentioned above, rendered impossible by some venoms in two ways: (1) action upon the nerve-cells in the central nervous system; (2) interference with the passage of nervous impulses at the nerve-muscular junctions of the phrenic nerve-endings. Most snake-venoms possess only the former action, but those of the *Enhydrina*, cobras, and kraits are endowed with poisons operating in both ways. In the case of those venoms possessed of both actions



the influence upon nerve-cells is the more rapid and important ; so that it is only under conditions of slower poisoning that the curara-like action can be demonstrated to its full extent.

The effect upon respiration of the venoms of those viperine snakes an analysis of the action of which has been undertaken—*Crotalus*, *Ancistrodon* (Weir Mitchell), *Daboia*, puff-adder, and *Lachesis* (Rogers)—is not so specific as in the case of the colubrine venoms. With these viperine poisons the effect upon the nervous system as a whole is less intense, and no individual group of nerve-cells appears to be strikingly picked out. When simultaneous records of respiratory movements and blood-pressure have been taken, the arterial pressure has been found to fall to a dangerous extent, at the same time that the respiratory tracing has shewn diminution in rate and amplitude. The dependence of respiratory activity upon the arterial pressure has been shewn in the case of chloroform poisoning by Drs. L. Hill and Embley, so that it is rather difficult to ascertain exactly how much direct paralysis of respiratory cells co-exists when complicated by the indirect effect of a greatly lowered blood-pressure. What appears to happen is that when the blood-pressure has fallen to a sufficient extent, the respiratory cells, which are now half-paralysed, cease to be active and respiration fails. In no case has absolute paralysis of respiration been observed in association with circulatory efficiency.

*Effect of Venoms upon the Circulation.*—Venoms may influence the circulation either by their direct action upon the muscle of the heart or arterioles, or indirectly through the nervous system.

*Action on the Isolated Heart.*—Most venoms, unless they are much more concentrated than ever occurs in cases of poisoning, exert but little influence upon the isolated heart of cold-blooded animals. On the other hand, the efficiency of the circulation is soon impaired in experiments with all venoms, except those of cobra and *Bungarus caeruleus*, but to what extent this may be due to direct action upon the heart itself has not been clearly shewn, for all venoms ultimately paralyse the cells of the nervous vasomotor mechanism.

The poisons of the cobras and the common krait, *Bungarus caeruleus*, and to a much less extent the venoms of *Enhydrina ratakadien* and *Notechis scutatus*, the Australian tiger-snake, have, however, an effect upon cardiac muscle which was first observed by Sir Lauder Brunton and Sir J. Fayrer, and has recently been more completely studied by Sir T. R. Fraser and Major Elliot, who found that cobra-venom in dilutions of 1 in 10,000,000 and upwards exerts a stimulating action (induces increased tone) upon the isolated hearts of frogs or mammals. As the strength of the poison in solutions with which the heart is fed is increased, the effect becomes more marked until the heart is brought to a standstill in systole.

*Direct Action upon the Arterioles.*—The venoms of the cobra and the common krait exert a stimulating action upon the muscle of the vessel-wall similar to that just described in the case of cardiac muscle. This

direct action of these poisons is the reason why the blood-pressure is maintained at or above its normal height during poisoning with these venoms. Major Rogers has shewn that constriction of arterioles is also produced by the local action of the venom of Russell's viper.

*Effect upon the Blood-pressure.*—Records of the blood-pressure during poisoning by quite a considerable number of snake-venoms have been made. Many of the older results, and especially those in which the poison was injected intravenously, have been erroneously interpreted, as it was not known that many venoms produced intravascular clotting. This source of confusion must be eliminated before the direct effect of a poison upon the heart or vasomotor mechanism can be estimated. More recent workers have been able to obviate this difficulty.

The venoms of cobras exercise a peculiar effect upon the blood-pressure; this is due to their stimulating action upon the heart and blood-vessels, and the simultaneous rapid paralysis of the respiration before the other nervous centres. Consequently the picture presented is a record in which the blood-pressure remains at its normal height, or even slightly raised, until the respiratory movements are no longer adequate to aerate the blood sufficiently. The vasomotor and vagus centres which are not yet paralysed respond to the stimulus, the pressure rises, and the heart slows much as in asphyxia in a partially curarised animal. If artificial respiration be not carried out, the pressure slowly falls, as the heart fails from want of oxygen, to 20-30 mm. of mercury. If artificial respiration be maintained, the pressure keeps up sometimes for hours and only slowly falls. In experiments with the venoms of other colubrine snakes, such as *Enhydrina*, *Bungarus fasciatus*, *B. cœruleus*, *Notechis scutatus*, *Notechis pseudechis*, and *Acanthophis antarctica*, the results are different. In all of these cases the blood-pressure, even if well maintained at first, soon shews signs of failing *pari passu* with the paralysis of respiration; and although in some cases respiration may cease before the onset of marked circulatory depression, the latter soon follows, and artificial respiration is incapable of preventing a slow fall of blood-pressure to zero. Simultaneously with the fall in pressure a rise in the volume of the spleen or bowels has been observed, so that vasomotor paralysis is in large part responsible for the failure of the circulation.

The effect of viperine poisons upon the blood-pressure is to produce a considerable fall, which is to a large extent due to the action of these poisons upon the nervous vasomotor mechanism. The influence of the venoms of *Daboia*, puff-adder, *Lachesis*, and *Crotalus* upon the circulation is more striking than the effect upon the respiration, and the great depression which is a symptom of viperine poisoning may no doubt be explained in this way.

The effect of all the venoms which cause fall of blood-pressure is exaggerated when they are introduced intravenously.

*Action of Venoms on Blood-plasma.*—Most, if not all, of the poisons of viperine snakes, and the venom of a number of the Australian colubrines also, contain fibrin-ferments. These venoms cause clotting in

every kind of plasma in which coagulation has been suspended by artificial means; and if introduced with sufficient rapidity, as by intravenous injection, into the blood-stream of an animal, whether reptile, amphibian, bird, or mammal, intravascular clotting takes place and consequently cessation of the circulation. This is indeed the way the death of small animals, which form the prey of these snakes, is usually brought about. The snake injects a large quantity of venom, relatively to the minimal lethal dose, and the effect is the same as when smaller quantities are introduced directly into a vein. In snake-poisoning in man, however, these fibrin-ferments do not play an important part, as they do not reach the circulation with sufficient rapidity to produce general thrombosis. The effect upon the plasma in these circumstances is in the opposite direction, and the blood is found to possess diminished coagulability, or even to fail to clot at all. This negative phase only occurs in the living body. It establishes a kind of immunity against the ferment, for when the blood has arrived at this condition the further addition of large quantities of ferment fails to cause clotting. The mechanism of this immunity has not been ascertained.

The poisons of the cobras contain a substance the direct action of which prevents the coagulation of blood. This effect is manifested either in the body by the presence of a non-coagulable blood after injection of cobra-poison or *in vitro* upon oxalate- or citrate-plasma. Plasma kept fluid by either of these means, to which cobra-venom has been added, fails to clot on the subsequent addition of lime. The venoms of the other Indian colubrine snakes exert no influence upon blood-plasma.

*Effect of Venoms on Blood-corpuscles.*—The effect of crotalus-venom upon red blood-corpuscles was pointed out by Weir Mitchell and Reichert, who found that the red corpuscles lost their biconcave form and became spherical and sticky, so that they adhered together in strings. Subsequently the hæmoglobin dissolved out and they became invisible. Ragotzi observed the same dissolution of corpuscles with cobra-poison, and Feoktistow with the poison of *Pelias berus*, the common viper of Europe. The venoms of the Australian colubrines, *Notechis scutatus* and *N. pseudochis*, possess powerful hæmolytic action, and hæmolysins have in recent years been shewn to exist to some extent in the poisons of all the snakes that have been investigated.

The activity of these hæmolysins for the corpuscles of different animals varies enormously, and the venoms of some snakes contain hæmolysins more potent for the corpuscles of one species of animal, whereas those of another snake are more active in hæmolysing the blood-corpuscles of a different species. Hæmolysis is seldom, however, a marked feature of human poisoning by any venom, because the dose of a venom necessary to destroy life by other means, *e.g.* by paralysis of respiration, is very much less than the quantity necessary to produce any very extensive destruction of blood-cells.

The most marked hæmolysis *in vivo* is produced by the venom of the

Australian black snake *Notechis pseudochis*, when sub-minimal lethal doses are injected into dogs. In some cases the red cells were reduced in two days to one half their original number, and the urine was saturated with hæmoglobin. This large effect was not seen when other animals were experimented upon.

In recent years light has been thrown upon the mechanism of venom hæmolysis by Flexner and Noguchi, and Kyes and Sachs, who have shewn that the phenomenon is in many respects analogous to serum hæmolysis and bacteriolysis. On this account experiments with venoms have attracted an additional interest, as they have been found suitable for employment in fundamental experiments concerning cytolysis in general. Flexner and Noguchi found that certain washed blood-corpuscles were not hæmolysed by venom, but that when the previously separated serum was added solution took place. They concluded, therefore, that in the process of hæmolysis venoms act only as intermediary bodies or amboceptors, and require a complement to complete the reaction. This interpretation of the action of hæmolysins in snake-venom has been confirmed by Kyes and Sachs, who found, however, that the washed cells of some animals, *e.g.* dog, horse, man, were hæmolysed to some extent by cobra-venom alone, and explained this as due to these cells containing complement within themselves. In further experiments they shewed that lecithin was capable of acting as complement in the case of cobra-venom, so that their explanation of endo-complement is probable. One of us (G. L.) has confirmed and extended these observations on venom hæmolysis, and has also demonstrated that in the absence of complement or complementoid the hæmolytic amboceptor of venom is not taken up by the red cell.

*Action of Venoms upon White Blood-cells.*—The effect of most venoms upon leucocytes has not been studied. The effect of 1 per cent solution of the venoms of two Australian snakes upon the white cells of the frog and mammals upon a warm stage shewed that after a few minutes all movements ceased, the cells became granular and the nuclei more distinct, and in half an hour to one hour many of them were dissolved. Besides inhibiting the movements of leucocytes outside the body, these snake-venoms also interfere with their vital activity in the body, as shewn by the following experiment, which is one of a series with similar results. Two small pieces of sterilised sponge, about 1 mm. cube, were aseptically introduced into the abdominal wall of a guinea-pig. One of these little sponges had been soaked in 7 per cent solution of NaCl containing 1 per cent of venom, the other in the saline solution without the venom. Both sponges were pushed about a centimetre away from the incision, which was afterwards drawn together by a horse-hair suture and covered with collodion. After two hours œdema occurred around the venom-containing sponge, but not around the other. At the expiration of five hours the animal was killed, and both sponges were carefully withdrawn and plunged into absolute alcohol. Sections of the two sponges treated in the same way presented very different appearances. The

control was infiltrated with leucocytes which stained well with ordinary nuclear stains; the other contained leucocytes near the margins only, and many of these were broken down and took the stain badly or not at all. From these sponge experiments it was concluded that whereas into the control sponge the leucocytes by their amœboid movements could penetrate unharmed, in the other sponge their activity was paralysed; they succumbed, and were eventually disintegrated by the solution of the venom.

Flexner and Noguchi have since made a more complete and accurate study of venom leucolysis. They used the poisons of cobra, rattlesnake, and moccasin, and found .002 per cent solutions effective *in vitro*. After a time, depending upon the concentration of the venoms, motility ceased, followed by granulation and disintegration. They found that the leucolysin was distinct from the hæmolysins in these venoms, and that the process was of the same nature as hæmolysis, and required the addition of a complement, which was contained in the animal's own serum.

*Effect on the Blood-vessels.*—The occurrence of hæmorrhages both locally and all over the body is most marked after poisoning by the venoms of South American vipers of the species *Lachesis*. It is particularly characteristic of the action of the Crotalinæ, and is a prominent feature of all viperine poisoning. It also occurs, but to a small extent, with some of the Australian colubrids. Weir Mitchell first investigated the mechanism of the phenomena of hæmorrhagic extravasation. He prepared the mesentery of a warm-blooded animal for microscopical observation on the warm stage, and then applied crotalus-venom to it. He noticed an almost immediate dissolution of the continuity of the capillary walls with which the poison came in contact. This occurred suddenly, and was not preceded by any diapedesis of white corpuscles. The blood escaped, without previous indication, from those capillaries which were nearest to an arterial twig, and in which, therefore, the hydrostatic pressure was highest. Ligation of the vessels going to the part prevented further hæmorrhage.

Flexner has given the name of *hæmorrhagins* to the constituents of venoms which destroy the continuity of vessel-walls, and looks upon them as cytolytins for endothelial cells of blood-vessels. Careful histological observations of the effect of hæmorrhagins shew that there is a definite solution of continuity of the endothelial lining of the capillaries, so that this view is no doubt correct.

*Examination of the Gases in Blood after Poisoning with Venom.*—Beyond setting it free from the corpuscles, snake-venoms exert no influence on the hæmoglobin of the blood: it is still capable of taking up oxygen and parting with it as under normal conditions. In an animal poisoned with the venom of the Australian black snake the quantity and also the tension of oxygen in arterial blood, except immediately preceding death when the respiration and circulation were failing, were found to be approximately normal. The absolute quantity and tension of CO<sub>2</sub> were both usually a little higher than before the injection. This is easily



explained by the diminished respiratory movements and retarded circulation. Artificial respiration reduced the excess to a small extent. As death approached, both the tension and the quantity of  $\text{CO}_2$  contained in the blood increased greatly from the same cause.

*Influence of Snake-venoms on the Germicidal Action of Serum.*—Went Mitchell has frequently pointed out that, as a general rule, the characteristic local extravasations of crotalus-poisoning suppurate or become gangrenous, and that bodies of animals dead of rattlesnake poisoning putrefy with extreme rapidity. Feoktistow made the interesting observation also that the bloody effusions in the pleura and pericardium sometimes contain micro-organisms immediately after death; and that cultures of these organisms, when injected into healthy animals, produce no effect. Ewing repeated some of Nuttall and Buchner's observations on the germicidal power of serum, and instituted a series of comparative experiments with the plasma or serum of animals poisoned with crotalus-venom; he found that, after poisoning with crotalus-venom, the normal germicidal power of rabbit's serum for *B. anthracis* and *B. coli* was entirely lost.

Experiments made in Sydney with the venoms of *Notechus pseudocobra* confirmed these results of Ewing. In 1902, Flexner and Noguchi made a further study of this action with the venoms of the cobra, moccasin, copperhead, and rattlesnake, in the light of facts which had been ascertained concerning the phenomena of bacteriolysis. They experimented with *B. anthracis*, *B. coli*, and *B. typhi*, and the serum of the rabbit, and showed that the action depended upon the presence in venoms of bodies of the nature of anti-complement.

**Morbid Anatomy in Man.**—The number of carefully recorded autopsies is small. In cases of death from *cobra-bite* rigor mortis occurs as usual. The areolar tissue in the region of the bite is infiltrated with pinkish fluid, and the neighbouring vessels are injected. The blood is often fluid, and when examined by the microscope directly after death it presents no changes. The brain appears to be normal; but the veins of the piamater are usually gorged with blood, and the ventricles often contain turbid fluid. The lungs are usually congested, and the lining membrane of the bronchi is intensely injected. The appearance of the kidneys varies from the normal to one of excessive congestion.

After death from poisoning by one of the *viperine snakes*, the region of the bite is the seat of intense cedema and extravasation of blood. If the poison be introduced into the subcutaneous tissue the underlying muscles are frequently disorganised and even diffuent from extravasation of blood in their midst. Hæmorrhages may also be found in any of the organs and along the alimentary tract. The kidneys are acutely congested or hæmorrhagic. The blood is fluid.

Autopsies in cases of bite by *Australian species of snakes* present, as a rule, the same appearances as those detailed in cobra bite. The blood is almost invariably fluid, but may contain a few soft coagula. The lungs may be the seat of hæmorrhages, in cases in which blood has escaped



from mucous tracts during life these surfaces are intensely congested and hæmorrhagic. The nervous system merely shews hyperæmia.

In the case of bites by viperine snakes, should the patient survive for some days the region of the bite is often the seat of a large slough or even of a rapidly advancing emphysematous gangrene. This local condition will of course depend upon the species of bacterium which has become implanted in the tissues already devitalised by the venom.

**Symptoms of Snake-bite in the Human Subject.**—We have already pointed out that venoms are very complex substances, each made up of several constituents of different physiological action, and that the dissimilarity in the effects produced upon man and animals by the different venoms is entirely due to the proportions in which the different groups of toxic substances occur in each poison. The symptoms, in cases of snake-bite, also vary somewhat according to the amount of venom injected and the site of injection, in so far as this latter influences the rapidity of absorption of the venom. The physiological actions and symptoms produced by venoms can only be roughly classified into two groups corresponding to the colubrine and viperine families. So that it is necessary to consider separately the symptoms seen in cases of intoxication from the venoms of some of the more important species, the bites of which are dangerous to life.

*Cobra-bite.*—The first symptom is a sensation of burning pain, more or less severe, at the seat of inoculation. The spot soon becomes red, tender, and swollen. An interval of about half an hour usually occurs before the patient experiences any constitutional symptoms: he then feels intoxicated, sleepy, and weak in the legs; the weakness increases until he is unable to stand. Profuse salivation, paralysis of the tongue and larynx, with inability to speak or swallow, soon supervene. Nausea and vomiting are of frequent occurrence. The paralysis now becomes more general and decided; the patient lies on his back, incapable of movement; his breathing becomes slower and the respiratory excursions diminish; he appears to be conscious, but unable to express himself; the action of the heart is quickened, but of fair strength. At length the breathing ceases, with or without convulsions, and the heart soon stops. Up to or immediately preceding the respiratory cessation the pupil remains contracted and reacts to light. Should the patient survive the paralytic symptoms he returns rapidly into a state of complete health. There are occasional discharges of blood from mucous surfaces, but the urine never contains albumin.

*Bite of Bungarus ceruleus (krait).*—There is no doubt that bites from this snake are extremely dangerous, and that a considerable percentage of the total deaths from snake-bite in India, especially in Northern India, is due to it. The symptoms seen in cases of krait-bite are somewhat similar to those already described in cases of cobra-venom intoxication. In a recent case in a soldier in India, of which we have notes, the chief symptoms observed were paralysis of articulation, embarrassed and stertorous breathing, and semi-consciousness.

There was no local swelling or reaction at the site of the bite, which was on the ring finger. Death took place about eight hours after the bite.

*Bite of Bungarus fasciatus.*—No authentic cases of bites from this snake have been described in the human subject. The symptoms, therefore, which would be met with can only be deduced from those which have been observed in animal experiments, especially in monkeys. If a large amount of this poison be injected directly into the circulation, intravascular thrombosis results and the symptoms observed are due to this pathological condition. As, however, this can practically never happen in nature we need not discuss it further. The ordinary cases may be divided into two classes; those in which death takes place within the first forty-eight or seventy-two hours after the bite; and those in which death is delayed for from six to twelve days. In the first class of acute nervous cases the symptoms are similar to those seen in cobra-venom intoxication. Death is due to paralysis of the respiratory centre. The local reaction is much less than in cases of cobra-bite—in fact, little or nothing is to be observed at the site of the bite. In the second class of cases we have, however, to deal with a condition which is never seen in cobra-venom poisoning, nor, in fact, in poisoning with any other venom with which we have worked. In these cases death is delayed for from six to twelve days. There is, as a rule, an interval after the bite, varying from two to six days, in which no symptoms are observed. After this interval a comparatively chronic disease, which almost invariably ends fatally, begins. The symptoms which arise during this late period of intoxication are not in the least like those seen in the acute cases of poisoning, either with cobra-venom or with the venom of *Bungarus fasciatus* itself. There are loss of appetite and great depression; but marked muscular weakness and atrophy, extreme emaciation, and loss of weight are the prominent symptoms. There is also a marked diminution of the urine, and irregular elevations of temperature are sometimes observed. Purulent discharges from the eyes, nose, and rectum occur late. The emaciation, loss of weight, and muscular atrophy progress rapidly, and, as a rule, end in death after a few days of illness.

*Bite of Enhydrina valakadien.*—This species is the commonest of the sea-snakes; it is very abundant along the coasts of India and Burma to the Malay Archipelago and New Guinea. There are no authentic cases on record of bites in the human subject, so in this instance also the description of symptoms is taken from animal experiments. The symptoms observed in animals after injection of this poison are very similar to those of cobra-venom intoxication. The local reaction is however, very slight; and, further, there are no symptoms which point to any action of the poison on the coagulability of the blood-plasma or on the red cells. There is progressive paralysis accompanied by dyspnoea, which latter symptom is much more marked than in cases of cobra-venom poisoning; death is preceded by respiratory convulsions. The heart goes on beating for several minutes after the respiration has ceased.

*Bite of Rattlesnake.*—The pain of the wound is severe, and is speedily

followed by swelling and discoloration ; sometimes there is hæmorrhage from the wound. Constitutional symptoms occur, as a rule, in less than fifteen minutes. These consist in progressive prostration, which eventually becomes appalling, staggering gait, cold sweats, nausea and vomiting, quick and feeble pulse, dilated pupils, and slight mental disturbance. In this state the patient may die about twelve hours after the bite. If he recover from the depression the local symptoms begin to play a much more important part than in cobra-poisoning. The swelling and discoloration extend up the limb and trunk, and symptoms of general blood-poisoning set in with rise of temperature, puffy face, great weakness, and repeated syncope. The pulse is quick and feeble, and the respiration laboured. Sometimes the mind is clear ; sometimes there are restlessness and delirium. Death may occur in this stage, and is sometimes preceded by convulsions. The local hæmorrhagic extravasation frequently suppurates or becomes gangrenous, and from the results of this the patient may die even weeks afterwards. When the dose has been a less severe one the swelling may decline and pain disappear rapidly. Recovery from the acute symptoms is in almost every case sudden and astonishing when contrasted with the gravity of the symptoms ; within a few hours the patient, from being in a moribund condition, becomes bright and intelligent.

*Bite of the European Viper.*—The symptoms following the bite of the European viper resemble those of a small dose of rattlesnake-venom. The bite is immediately followed by local pain of a burning character ; the limb soon swells and becomes discoloured, and within from one to three hours great prostration, accompanied by vomiting and often diarrhoea, sets in. Cold clammy perspiration is usual. The pulse becomes extremely feeble, and slight dyspnoea and restlessness may be seen. In severe cases, which occur mostly in children, the pulse may become imperceptible and the extremities cold ; the patient may pass into coma. In from twelve to twenty-four hours these severe constitutional symptoms usually pass off ; but in the meantime the swelling and discoloration have spread enormously. The limb becomes phlegmonous and occasionally suppurates. Within a few days recovery usually occurs somewhat suddenly, but death may occur from the severe depression, or from the secondary effects of suppuration.

*Bite of Daboia russellii.*—This snake may be taken as the typical Indian viper ; it is very widely distributed throughout the Peninsula, Ceylon, Burma, and Siam. It is also found in the Himalayas up to 6000 feet at least. It is one of the most deadly snakes, and next to the cobra probably causes more deaths in India than any other snake. If daboia-venom be injected directly into the blood-stream, a condition which might happen in the case of a bite in man, violent convulsions rapidly set in and soon end in death. These symptoms are due to a more or less general intravascular thrombosis. When the poison is introduced into the subcutaneous tissues the symptoms may be divided into local and general. Locally there are very severe pain and rapid onset of swelling, which soon extends up the limb, if the bite is on an extremity ; there is

often a blood-stained discharge from the wounds. Ecchymosis is soon very apparent all round the site of the punctures.

The general symptoms are marked collapse, a small thready pulse, cold sweats, nausea, and vomiting, pupils dilated and insensitive to light, and often complete loss of consciousness. The patient may temporarily recover from these general symptoms, only to fall into a deeper state of collapse than before. Death often takes place within a short time after the infliction of the bite. If, however, recovery from this depression takes place, the local condition plays an important part in the subsequent history of the case. The swelling extends rapidly; there is a large extravasation of blood with much œdema all round the punctures. Extensive local suppuration and sloughing, malignant œdema, or tetanus may supervene; and the symptoms of these conditions may now be added to those due directly to the venom. These latter symptoms consist of œdema of the dependent parts, and hæmorrhages, often severe, from the rectum and other orifices of the body; albuminuria or hæmorrhage from the kidneys is a constant symptom. Rapid emaciation soon appears, and in the prolonged cases a profound anæmia and lethargy set in. There is an absence of paralysis and of any symptoms which might point to any direct action of the poison on the central nervous system. Death may be delayed for several days: this, however, depends more on the local condition. Recovery in these cases is not at all uncommon.

*Bite of Echis carinata.*—This is a comparatively small snake, although its poison is extremely active. The symptoms following its bite are similar to those of daboia-bite. The local swelling and hæmorrhagic extravasation are severe. As the amount of venom injected at each bite is comparatively small, recoveries are fairly common, and it is probable that the mortality from this snake is not large. Recently an authentic case came under observation in St. George's Hospital, Bombay, of which we have full notes. A man was bitten on the temple by an *Echis carinata*, which was in captivity in the Museum of the Bombay Natural History Society. He came under observation a quarter of an hour after the bite, and was then very frightened and had an anxious look on his face. The whole of the temple, on which two small punctures could be seen, was swollen and ecchymosed, the swelling extending to the side of the face and including the upper and lower eyelids. There was severe pain over the wounds. The blood which exuded from incisions made over the punctures was very liquid, and remained unclotted. Vomiting soon began and continued till death. The pulse was very small, feeble, irregular, rapid, and at times could hardly be felt at the wrist. Extreme restlessness and complete insomnia were marked symptoms. The extremities were cold and clammy. The patient remained conscious for many hours; but a short time before death, which took place twenty-five hours after the bite, he became unconscious and delirious. There were no hæmorrhages from any of the orifices.

*Bite of Australian Species of Snakes.*—The pain and local swelling which

follow a bite by one of the larger Australian colubrids are not usually severe. Constitutional symptoms appear in from fifteen minutes to two hours. The first symptom is almost invariably a feeling of faintness and an irresistible desire to sleep. On an attempt to walk the gait becomes staggering, and the weakness in the legs increases until the patient is unable to stand alone. Alarming symptoms of prostration then supervene, and are often accompanied by vomiting. The heart's action becomes extremely feeble, and the pulse thread-like and uncountable, the extremities are cold and the skin blanched. The respiration, which at first is somewhat quickened, becomes shallower from hour to hour as the coma increases. Sensation is blunted, and eventually stimulation of the nerves of special sense ceases to evoke any reaction: the pupil is widely dilated and insensible to light. In this state death may occur from gradual cessation of respiration; it is sometimes preceded by convulsions. The heart, which has become extremely feeble in its action, may sometimes be felt to beat for a few seconds after the cessation of respiration. In some cases hæmorrhagic extravasation also occurs from some mucous surface; so that the patient coughs or vomits blood, or passes it by the rectum or kidneys, but this is unusual. Albuminuria has been generally found when looked for, and may be accompanied by blood or blood pigment in the urine. If the patient survive the coma, recovery is complete; and, as a rule, is rapid and without any secondary symptoms.

**Prognosis**—If we assume that the susceptibility of man to snake-poisons is weight for weight not greatly different to that found for a monkey or a dog, then by reference to the tables above, setting forth the quantity of venom which different snakes can eject at one time and their minimal lethal dose, it is obvious that the larger serpents can discharge many lethal doses, in the case of the cobra 20 lethal doses, into a person bitten. Nevertheless, the mortality in persons bitten by the larger snakes of India and South America would not, from the scanty records available, appear to be more than 30 per cent. If these figures represent the truth, either the susceptibility of man, weight for weight, is greatly less than that of most other animals, or else in the circumstances in which a snake bites a man the reptile is seldom able to inject its full charge. The former alternative seems to us unlikely on general grounds, and we incline to the latter view as the more probable. When a snake bites a man, it is generally in a hurry and it is not permitted to gnaw away at its victim in the same way as it is encouraged to bite a watch-glass for the purpose of collecting venom in the laboratory.

**Treatment of Cases of Snake-bite.**—When a person has been bitten by a poisonous snake our efforts to influence the result should take two directions: (1) to prevent the absorption of the poison; (2) to counteract or lessen its effects on the organism.

(1) With the first object a ligature should immediately be placed on the limb above the situation of the bite; the ligature must of course be applied where there is only one bone and not on the forearm or lower leg. Wall strongly recommends a stout india-rubber band as being by



far the best material for use as a ligature ; but in ordinary circumstances only a portion of clothing would be available, and answers quite well. The ligature must be tightly applied ; this is easily attained by passing a stick under the ligature and twisting it. The action of the ligature is to delay the absorption of the venom for just so long as it may be applied, and in the case of venoms, such as those of the cobra and the krait, which contain no fibrin-ferment, this is all that is accomplished by its use. In those venoms, however, which, like *Echis carinata* and many of the Australian snakes, contain fibrin-ferment, it operates in another way and one which would hardly have been expected. Experiments with the poisons of *Notechis scutatus* and *N. pseudochis* have shewn that six times a fatal dose of these venoms may be injected into the leg of a rabbit and be followed by little or no constitutional disturbance, provided an elastic ligature be applied immediately afterwards above the seat of inoculation and allowed to remain on for twenty minutes. These experiments have been frequently repeated, and on dissecting down onto the situation of the injection it was discovered that the blood and lymph in the immediate neighbourhood of the seat of inoculation were completely solid, so that the poison was temporarily shut up and could only be slowly absorbed subsequently. Moreover, it is not unlikely that a good deal of it became combined with the cells in the locality. On repeating these experiments with the same venoms which had been exposed to a temperature of 75° C., so as to destroy the fibrin-ferment, the only result of ligaturing the limb was to delay the onset of symptoms and death of the animal for so long as the ligature had been applied.

Having by means of the ligature insured that no more poison is absorbed, the next step is to destroy or remove what poison still remains deposited locally, with the object of preventing as much as possible of the venom from entering into the general circulation on removal of the ligature. There is great difficulty in thoroughly accomplishing this object. Wall has correctly pointed out that the poison is deposited not in the skin itself but in the areolar tissue beneath, and that as the skin is as a rule freely movable over the parts below, the fangs may have dragged it away from its proper position before the poison is injected. In this way it may happen that the poison is not deposited immediately beneath the punctures. Keeping this possible contingency in view, Wall strongly recommends careful and deep dissection with the knife of all the parts likely to contain the poison. The dissection must be free in all directions, especially so in the direction of the lymphatic and venous return. In the case of the fingers, hand, and such parts it should be carried right down to the bone. After this free and careful dissection, the wound should be freely washed out with a strong solution of permanganate of potash, which will destroy any poison with which it comes in contact. Many other methods have been recommended for the destruction of the poison locally. The injection of any substance, such as bleaching-powder or chloride of gold, as recommended by Calmette, can be made by guess-work only, as we do not know exactly where the



poison lies ; and the solution, instead of following the venom, will take the line of least resistance in the tissues, and if the patient recover will produce a nasty slough. Washing the punctures with any kind of solution is of course futile. Wall also considers that the application of any destructive agent to an incision through the wounds is almost useless ; he found that such a method sometimes succeeded after the injection of the poison with a syringe, but was without avail after the natural bite of a snake. The same difficulty will be met in the method lately advocated by Sir L. Brunton, Sir J. Fayrer, and Major Rogers, in which it is advised that an incision be made over the punctures with a lancet-shaped blade and crystals of permanganate of potash then be rubbed in. Major Rogers found this method successful in the case of cats, but in these experiments he knew accurately the direction taken by the point of the needle ; in practice we fear that it will only be by chance that the permanganate reaches the poison, which may be placed deeply in the areolar tissue and at some distance from the punctures. The method, therefore, must be much less efficacious than that of free dissection, as recommended by Wall, followed by swabbing out of the wound with a strong solution of permanganate of potash. To suck the wounds is absolutely useless.

(2) As well as attempting to remove and destroy as much as possible of the venom which has been deposited locally, we must endeavour to render innocuous any poison which has been already or is likely to be absorbed into the general circulation. Various remedies have been suggested and strongly recommended for the treatment of cases of snake-bite. Alcohol, ammonia, and strychnine have been strongly advocated ; the two latter especially in Australia. But all experimental work, as well as practical experience, prove that none of these medicines is of the slightest use as an antidote to snake-venom. In India numbers of quack medicines are year after year recommended, only to be found quite useless when tested experimentally. It is quite unnecessary to consider these remedies.

*The Serum Treatment of Snake-poisoning.*—While all these empirical methods have failed us in the treatment of cases of snake-bite, recent research has shewn that along the line of serum-therapeutics lies the true antidote for snake-venom intoxication. In 1894 Calmette established that an animal that has been treated over a length of time with the venom of a poisonous snake, such as the cobra, yields a serum which is antitoxic towards that poison. On account of the interest and importance of the subject, a short description of the work which has led up to this result will not be out of place.

The belief that by the repeated injection or eating of snake-poisons some amount of immunity can be established, has been current from very ancient times amongst the inhabitants of many lands where poisonous serpents abound. Sir T. R. Fraser has collected a number of these legends and presented them in an interesting introduction to his lectures on Immunisation against Serpent's Venom, delivered at the Royal Institution

(*Nature*, April 23, 1896). That individuals who have repeatedly been bitten by snakes, such as some native snake charmers and others in the habit of manipulating these reptiles, may possess a considerable amount of resistance, is undoubted. We are aware of the case of a European in Australia who used to manipulate *Nolechis scutiger* with impunity, and who was bitten on more than one occasion in our presence, with but slight manifestation of ill effect. This individual was, however, under the impression that his immunity was equally valid for other poisonous species, and on being bitten by a large specimen of *Denisonia superba*, in endeavouring to secure it, died on the following day.

Immunity against snake-venom by experiments upon animals was first obtained by Sewall, who shewed that repeated injections of small doses of rattlesnake-poison establish a resistance to the poison. Subsequently Kanthack succeeded in obtaining some resistance to cobra-poison, but was unable to obtain complete immunity. Phisalix and Bertrand in 1893 induced some immunity in rabbits by repeated injections of the European viper's venom, which had previously been heated to 80 C., and found that the serum of the animals thus treated was possessed of curative properties. In 1894 Calmette published an account of his extended researches on this subject. By patiently immunising horses against cobra-venom, Calmette succeeded in producing sufficient antitoxin in their serum to be of some practical value. In the following year Sir T. R. Fraser, who had also been investigating the same problem, published a confirmation of Calmette's results and some further points of importance in relation to the nature of the protective action of the serum. The results of these two observers, working quite independently of each other, shewed that a solid immunity could be obtained by repeated, long-continued injections of snake-venom, and that the serum of an animal treated in this way contained antitoxic substances. Calmette then proceeded to produce an anti venomous serum in sufficient quantity for therapeutic purposes. This serum was prepared with a mixture of snake-venoms, in which mixture, however, cobra poison greatly preponderated.

*The Specificity of Antivenomous Serums.*—Calmette asserted that the serum prepared at Lille was active against the venoms of all species of snakes, a claim based on the conception that all snake venoms are alike in physiological action and differ from one another only in their degree of toxicity. In the light of more recent research, this conception is, as we have seen, no longer tenable, and the contention regarding the universal applicability of the serum prepared at Lille has been shewn to be without foundation. This serum was found inadequate to preserve animals against injections of the poison of the Australian tiger snake, although it possessed a certain neutralising value for the neurotoxin of this poison. Subsequent experiments in Sydney shewed that the same was true as far as the poisons of other Australian snakes were concerned. In India it was shewn that the Lille serum, while active for cobra-venom, had no

neutralising effect for the poisons of the following snakes, namely, *Daboua russelli*, *Bungarus fasciatus*, and *Echis carinata*.

Recently Calmette went so far as to admit that in some venoms there are two poisonous constituents, namely, a neurotoxin and a hæmorrhagin; and that the antitoxic serum prepared by injecting cobra-venom is without action upon this hæmorrhagin, but that such a serum is distinctly antitoxic to all the neurotoxins of other venoms. This hypothesis, however, is not in consonance with the facts which have been acquired by the careful testing, both *in vivo* and *in vitro*, of various serums prepared with pure unmixed venoms.

As this question of specificity or non-specificity of serums is of practical importance, results which have been obtained with six pure anti-serums are worthy of mention in some detail (1) a serum prepared by Tidswell with the poison of *Notechis scutatus*; (2) a serum prepared by one of us (G. L.) with cobra-poison; (3) a serum prepared by one of us (G. L.) with the venom of *Daboua russelli*, (4) a serum prepared by Noguchi with croतालus-venom; (5) a serum prepared by Noguchi with moccasin-poison, (6) a serum prepared by Brazil with lachesis-poison.

(1) Serum prepared with the poison of *Notechis scutatus*.—This serum tested *in vivo* has been shewn to be strongly antitoxic for its homologous venom, but to be without neutralising action for the venoms of *Pseudechis* and *Lucania*, two species of Australian snakes, the poisons of which have physiological actions apparently identical with those of the venom of *Notechis scutatus*. It has also been shewn to be without neutralising effect on the general actions *in vivo* of the poisons of the following colubrine species, cobra, king cobra, *Bungarus ceruleus*, *Bungarus fasciatus*, *Enhydrina malakulien*; and of the following vipers: *Daboua russelli*, *Echis carinata*, *Lachesis gramineus*, and *Crotalus durissus*. When this serum is tested *in vitro* against the hæmolytic action of the several venoms, the following result is obtained: it neutralises the venom of *Enhydrina malakulien* rather better than it neutralises the poison with which it has been prepared; also, it has a marked inhibitory effect on the action of cobra-venom and of *Echis carinata* poison; but it has no inhibitory effect on the hæmolytic action of other six poisons, namely, the venoms of the king cobra, of *Bungarus ceruleus*, of *Bungarus fasciatus*, of *Daboua russelli*, of *Lachesis gramineus*, and of *Crotalus durissus*.

Finally, this serum has been tested against the clotting action which several venoms exert on citrate plasma, that is to say, against the fibrin-ferment contained in the poisons. The results of these observations shew that, while the serum neutralises well its homologous venom and also that of *Notechis pseudochis*, it is quite inactive against three other poisons, namely, the ferment in the venoms of *Echis carinata*, of *Lachesis gramineus*, and of *Crotalus durissus*.

(2) Serum prepared with pure cobra-venom.—This serum, tested *in vivo* against the general actions of various poisons, is found to be strongly antitoxic for the venom used in its preparation; when used in large quantity it has a slight neutralising power for the venom of *Enhydrina*

*valakadien* ; further, it delays death in cases of intoxication with the venoms of the king cobra and of *Bungarus fasciatus*, but even when used in large quantities does not completely neutralise these poisons. This serum contains no antitoxic substances active against the venom of *Bungarus cœruleus*. It was also found to be without neutralising effect for the venoms of the following viperine snakes: *Daboia russellii*, *Echis carinata*, *Lachesis gramineus*, and *Crotalus durissus*.

Cobra anti-venom was found to be largely specific as far as the hæmolytic actions of the several venoms are concerned: thus, it neutralises its homologous venom in a marked degree; it prevents to a certain extent the hæmolytic action of the venom of *Bungarus cœruleus*, a relatively much greater quantity of serum, however, being required to effect this than in the case of cobra-venom; finally, it has no hindering effect at all on the hæmolysing action of eight other poisons, namely, the venoms of king cobra, of *Bungarus fasciatus*, of *Notechis scutatus*, of *Enhydrina valakadien*, of *Daboia russellii*, of *Echis carinata*, of *Lachesis gramineus*, and of *Crotalus durissus*. The serum was further tested, also *in vitro*, against the anti-clotting action of both cobra and king-cobra venoms. It was found to neutralise well the venom of the cobra, but to have little or no effect on king-cobra poison.

(3) Serum prepared with the venom of *Daboia russellii*.—This serum has also been tested both *in vivo* and *in vitro*. When tested *in vivo* against the general actions of various poisons, it was found to have no effect whatever on any of five colubrine venoms, namely, the venoms of the cobra, king cobra, *Bungarus cœruleus*, *Bungarus fasciatus*, and *Enhydrina valakadien*; to neutralise well its homologous venom; to have a certain but not very marked neutralising effect on the venom of another viper, namely, *Crotalus durissus*; to have no antitoxic action for the venom of a closely allied viper, *Echis carinata*, nor for that of another Indian viper, *Lachesis gramineus*. When tested *in vitro* against the hæmolytic actions of several venoms, it was found that this serum has no hindering effect whatever on the venoms of six colubrine snakes; that it neutralises equally well the venom with which it was prepared and the venom of *Echis carinata*; that it has a considerable but less neutralising effect on the venom of *Crotalus durissus*, but no hindering effect on the poison of *Lachesis gramineus*. Further, when tested *in vitro* against the fibrin-ferment actions of various poisons, it was found that, while the serum neutralises well its homologous venom, it has no effect on the poisons of four other species, one colubrine and three viperine, namely, *Notechis scutatus*, *Echis carinata*, *Lachesis gramineus*, and *Crotalus durissus*.

(4) and (5) Serums prepared with crotalus-venom and with moccasin-venom.—The details of the testing of these two serums have not been published in a complete and full form; but the data which are available are clearly of the same nature as those obtained with the three serums mentioned above.

(6) Brazil found that the Lille serum was unable to save animals poisoned with lachesis and crotalus venoms; that his serum prepared

with the venom of lachesis was without action upon crotalus-poison, but that the anti-crotalus serum did possess some action against the venom of *Lachesis lanceolatus* as well as that of crotalus.

All these careful and detailed observations point to the same conclusion, namely, that, both in *in vivo* and *in vitro*, anti-venomous serums are highly, but not strictly specific.

The neurotoxin of cobra-venom is evidently somewhat different from that of the king cobra and *Bungarus fasciatus*, and quite different from that of the common krait (*Bungarus caeruleus*). Further, it is also clear that the hæmolytic constituents, the hæmolysins, differ markedly from one another. The same can be said of the fibrin-ferments of the various venoms. In short, Calmette's conception of the identity of neurotoxins, etc., is not justified by the facts; on the contrary, it is clear that identity in physiological action does not justify the assumption that a serum prepared with one venom will neutralise another. Megatheriolysin and tetanolysin both dissolve corpuscles, but a serum prepared against one is without effect upon the other.

The bearing of this conclusion on the problem of the serum-therapeutics of snake-bite is evident, for at the outset we are met with the almost insurmountable difficulty that only the specific anti-serum will be of use in a case of snake-venom intoxication. Now, in the first place, it seems almost impossible to collect these various venoms in quantities sufficient for the purpose of immunisation of large animals; and, in the second place, granted that it were possible to prepare anti-serums for the different poisons, the practical use of these would be beset with difficulty. For when a person is bitten by a snake he is rarely able to tell the species of snake which has inflicted the bite; furthermore, as an anti-venomous serum, to be of much practical utility, must be injected before any symptoms of intoxication have set in, the medical man who is called on to treat a case of snake-bite is not as a rule in a position to form an opinion, either from the history of the case or from the symptoms, as to the nature of the venom which has been injected. Probably the solution of this difficulty will lie in our being able ultimately to prepare a polyvalent serum with the venoms of the commonest and more deadly snakes. This principle is carried out to a limited extent at Lille; and from the Pasteur Institute of India a serum is being issued which is prepared by immunising horses with the unheated poisons of the cobra and the daboia, the two snakes chiefly responsible for the 20,000 or more deaths which occur annually from snake-bite in India. So far it has been found impossible to procure enough venom from the other Indian species to immunise large animals.

*The Dose of Serum Necessary.*—Calmette considers that 10 c.c. of the Lille serum is sufficient in most cases of snake-bite; but that if the treatment is delayed, or if the snake is a cobra or a krait, 30 c.c. should be used. He recommends that the injection should be given subcutaneously unless symptoms are already present, in which case an intravenous injection of 10 or 20 c.c. is required.



For reasons which will appear below, we are convinced that these small quantities are quite insufficient in the case of the cobra, against which the Lille serum is particularly antitoxic. In order to arrive at an accurate therapeutic dose of an anti-venomous serum three factors must be determined: (1) the neutralising power of the serum, that is to say, the exact amount of serum which can neutralise a given amount of venom; (2) the amount of poison which the snake can inject; (3) the quantity of venom the injection of which a man can survive.

Two c.c. of the Lille serum are stated to have the power of neutralising 1 milligramme of dried cobra-venom, and the serum issued by the Pasteur Institute of India is double this strength, or 1 c.c. neutralises 1 mg. of cobra-venom. If this is expressed in terms of the number of fatal doses for a guinea-pig of 250 grammes which can be neutralised by 1 c.c. of serum, a comparison may be drawn between the relative potency of anti-venom and the antitoxins for diphtheria and tetanus. Expressed in this way, 1 c.c. of the Indian serum neutralises only 10 minimal fatal doses for a guinea-pig of standard weight. On the other hand, 1 in every 4 horses will produce a diphtheria antitoxin, 1 c.c. of which, when tested under the same conditions, will neutralise 100,000 minimal fatal doses of toxin, or, if immunised against tetanus, will furnish tetanus antitoxin, 1 c.c. of which will neutralise 200,000 minimal fatal doses. It will be seen at once that, compared with these antitoxins, anti-venom is very weak indeed; in fact, if the other antitoxins were only possessed of such small neutralising power they would be of little practical use. It has not at present been found possible to immunise a horse so that it shall produce a serum of greater power, but possibly, by different methods of immunisation, serums of greater potency may be produced in the future.

We have thought it advisable to lay stress upon the real antitoxic value of anti-venoms, because we think this point has been very imperfectly realised.

The second point, namely, the amount of venom which a snake can inject, has been settled in the case of cobra and daboia venoms by actual experiment. In the cobra this amount varies from 200 to 350 milligrammes of dried venom, and in the case of the daboia it is somewhat less, namely, 150 to 250 milligrammes. These observations were carried out on fresh snakes recently caught. Calmette has made a series of experiments with cobras which had evidently been kept in captivity for some time; the greatest amount of dried venom which he was able to procure was 48 milligrammes, and the average amount was about 20 milligrammes. The therapeutic dose of serum recommended by him is calculated on this basis, and is evidently, therefore, much too small. It is obvious that in estimating the dose of anti-venomous serum to be used in the treatment of any case, say of cobra-bite, it should be borne in mind that the snake *may* have injected as much as 350 milligrammes, for the neutralisation of which quantity sufficient serum must be injected in order to save the patient's life. There must be, of course, many cases in



which less, probably a good deal less, venom would be injected, and a smaller amount of serum would then suffice; but there are no means by which this point can be estimated, and as treatment must be immediate there is no time to wait and watch the development of the case.

The third factor, the amount of venom which a man can survive, must next be considered. This can, of course, only be estimated roughly from experiments on animals. Basing our calculations on the results obtained with monkeys, we have arrived at the conclusion that for an average man the lethal dose of cobra-venom would be about 15 to 20 milligrammes, and of daboia-venom about 60 milligrammes. A man would, therefore, be able to survive slightly less than these amounts of poison.

Having as far as is possible arrived at the data on which the dose of serum to be used in any case of cobra- or daboia-bite rests, we have now to calculate what this dose ought to be. In the case of a cobra-bite, supposing the serum to be of such strength that 1 c.c. is able to neutralise 1 milligramme of pure cobra-poison, if the snake has injected the maximum amount of poison, namely, about 350 milligrammes, we can calculate that, in order to neutralise this quantity of venom and thus save the life of the patient, 350 c.c. of serum would have to be brought in contact with it. In the case of a daboia-bite a much smaller quantity of serum would serve the same purpose, as we have seen that this snake does not inject so much poison as the cobra, that the serum neutralises about double the amount of daboia-venom, and further, that the minimum lethal dose of daboia-venom by subcutaneous injection is much greater than that of cobra-poison. We can therefore calculate that about 100 c.c. of serum would be sufficient to neutralise the amount of venom which a full-sized daboia would be able to inject.

We have still to consider the method of injection, as these quantities of serum are the amounts which would be required to neutralise completely the venoms when they are mixed *in vitro* before injection. It has been shewn that as good results follow the simultaneous injection of a quantity of venom subcutaneously and of a neutralising dose of antivenom intravenously into an animal as are obtained when the venom and serum are mixed *in vitro* before injection. If, however, the serum is injected subcutaneously at the same time as the venom, it was found that from 10 to 20 times the neutralising dose of serum was required to save the life of the animal. Applying these observations to our present purpose, we arrive at the conclusion that in treating a case of cobra-bite in which the snake had injected the maximum amount of poison, we should have to inject 350 c.c. of serum intravenously or from 3500 to 7000 c.c. subcutaneously in order to save the life of the patient (!), and in the case of daboia-bites 100 c.c. intravenously or from 1000 to 2000 c.c. subcutaneously (!). Further, if symptoms have already appeared before treatment was begun, larger amounts of serum would be required to dissociate the poison from its junction with the cells. If the Lille serum is employed these quantities must be doubled, as it is only half the strength of that issued by the Pasteur Institute of India.

We have no desire to discourage the use of anti-venomous serums, once the poison has been absorbed, they are the only remedies available, but we wish to point out what is the real neutralising value of the serum and what may reasonably be expected from its use, and, further, to emphasise that quantities of 10 to 30 c.c., as recommended by Calmette, are hopelessly inadequate and only likely to lead to disappointment.

There are, of course, many cases of snake-bite in which for many reasons the snake does not inject anything approaching 300 milligrammes of poison, and for such cases treatment with a much smaller quantity of serum than those mentioned above would suffice. It is in fact probable that the great majority of cases would come into this latter category, but it must always be remembered that if the larger amounts of serum are not injected the treatment may fail because more than a lethal dose of poison remains unneutralised.

In the case of the bite from a snake for which a specific serum is available, e.g. cobra or daboia, this should always be injected. For reasons which have been set forth above, the following instructions should be followed:—

- (1) The injection should be made as soon after the bite as possible.
- (2) The injection should always be made intravenously.
- (3) At least 100 c.c. of serum should be injected.

In cases of bites from species of snake for which no specific serum exists, no benefit can be hoped for from the use of any other serum. As, however, it is extremely rare to be able to identify without any doubt the species of snake which has inflicted the bite, the serum treatment should be employed in India in every case of snake bite, on the chance that the snake was either a cobra or a daboia.

We are still far from the goal of an efficient polyvalent serum. It would be of the utmost value if we were able to obtain a stronger serum in a short interval of time without causing injury to the animals producing the serum. All workers on this subject are agreed that in order to procure a serum of sufficient strength for practical therapeutic purposes horses have to be treated over a period of from one year to a year and a half. Further, after each injection an abscess nearly always forms and sometimes there is most extensive sloughing. By modifying venoms so as to produce toxoids prior to injection, much perhaps may be done to obviate these objections. We have already mentioned that Flexner and Noguchi were able to immunise rabbits with crotales-venom which had been modified by treatment with weak hydrochloric acid. The solution of the problem of obtaining a serum which is efficient for most species of snakes is also hampered by the difficulty of obtaining supplies of poison sufficient for the immunisation of large animals. Thus in India, under the very best conditions and with the strong support of the Government of India, it has been found impossible to obtain any venoms, with the exceptions of those of the cobra and the daboia, in sufficient quantity to immunise animals. Until this difficulty has been overcome no progress can be made in this direction.

As regards the treatment of snake-bite other than by anti-venomous serums, little or nothing can be done beyond keeping the patient quiet and warm. Small doses of alcohol may no doubt be beneficial as a stimulant, but this end can be more effectually gained by ammonia or strychnine, and the employment of enormous doses of alcohol cannot receive too strong a condemnation. Major L. Rogers has recommended the use of adrenalin chloride in cases of bites from daboia and those snakes the poisons of which have a marked paralytic action on the vasomotor centre. On physiological grounds this drug should no doubt be of service in these cases. We are not aware that it has ever been used in practice.

To exhaust the patient when in the lethargic stage by walking him about incessantly cannot but be detrimental to his chances of recovery.

In conclusion, we have again to impress upon all who are called on to treat cases of snake-bite that every endeavour must be made to prevent absorption. An efficient ligature should be applied at once; then free dissection around the punctures, especially in the direction of the lymph and venoms return, should be practised, the wound being swabbed out with a strong solution of permanganate of potassium. These measures can usually be undertaken immediately, and in the present state of serum-therapeutics against snake-venoms more reliance should be placed on this local treatment than upon the injection of any anti-venomous serum.

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**ANIMAL PARASITES**  
**AND**  
**THE DISEASES THEY CAUSE**



## PSOROSPERMOSIS

By W. BULLOCH, M.D.

The name psorospermiosis has been loosely used in human pathology to denote sporozoic infections other than those caused by hæmosporidia. The name was originally given by Johannes Müller (1841) to certain vermiform-like bodies found in cutaneous diseases in fish (*Ψώρα*—the itch). These bodies were afterwards identified with parasitic protozoa and separated as a distinct group—the myxosporidia—although in medical writings the word psorosperm has been retained as a general designation for pathogenetic sporozoa not infecting the blood-corpuscles. Excluding these hæmosporidia, authentic cases of sporozoic infection in man are very rare, the parasites belonging mostly to the coccidiidea, while one or two have been referred to the sarcosporidia. In a large number of cases “psorosperms” have been described in which the diagnosis has been based on very slender foundations, and much of this work will not withstand the test of time. In recent years a great increase in our knowledge has resulted in reference to the structure and life-history of the sporozoa, and it is remarkable that the number of records of human psorospermiosis diminishes year by year. As the general structure and development of the sporozoa are dealt with on p. 61, it will be sufficient to refer to the human cases only.

**Coccidiosis.**—Unlike what obtains in several other vertebrates, cases of coccidiosis have rarely been observed in man.

**Infection with *Coccidium cuniculi* (Rivolta) (*C. oviforme*, *Eimeria stiedii* Demann).**—This sporozoon is ordinarily seen in the ripe sporont (oocyst) stage in the liver of the rabbit. It measures .033-.049 mm. long, and .015-.028 mm. wide, and is of oval shape. Originally described by Remak in this country, it was afterwards identified by Remak (1845) with psorospermiae. Discharged from the body the sporonts form four spores, each of which contains two sporozoites. The infection of the rabbit takes place by the ingestion of the oocysts or the spores which are set free in the stomach, and wander from the ductus choledochus into the bile-ducts, where they penetrate the epithelium and multiply by fission (schizogony).

Only some four or five human cases are accepted by experienced parasitologists as having been caused by this parasite. In Gubler's case,

observed in the hôpital Beaujon in 1858, a male, aged 45, suffered with digestive troubles and severe anaemia. The liver was found much enlarged, and a fluctuating tumour, diagnosed as a hydatid, was made out in the right lobe. At the autopsy about twenty cysts were found, one attaining a diameter of 12.15 cm. The contents were caseous and contained immense numbers of oval encysted bodies supposed to be the ova of a distomum, but regarded by Leuckart as true coccidia. Leuckart also refers to a case by Dressler in which the coccidia affected the liver, and to a case of Sattler in which the proliferated epithelium of the biliary canals was invaded by coccidia. In Sommering's collection in the University of Giessen, Paris found a human liver with coccidia in the bile ducts. In 1890, Quarry Silcock (38) showed at the Pathological Society an undoubted case of infection with *C. cuniculi*. The patient, a female aged 50, had suffered for six weeks from pains in the limbs, nausea, and sickness. There was tenderness of the spleen and liver, and fever existed with slight daily remissions. Death occurred from cardiac failure. At the necropsy the liver was found to weigh 83 oz., and contained a number of caseous foci, especially near the surface. Each focus had a well-marked inflammatory zone. A similar state of affairs also existing in the spleen, which weighed 16 oz. Microscopically the nodules consisted of masses of egg-like bodies with granular contents and well-defined capsules. By cultivating in water in a warm room sporosperms were developed. Amongst the doubtful cases are those published by Virchow, who found in the liver of an old woman a small mass filled with oval encysted bodies. Podwasserkb has reported four cases in which he found what he believed was a parasite (*Karyophilus hominis*) in the nuclei of the liver cells. J. J. Thomas has described the occurrence of coccidia in a bony formation in the brain. The lesion, which was of the size of a pea, contained in its interior numerous oval bodies, some of which shewed granular protoplasmic contents.

*Coccidium hominis* (Rivolta 1878) (*C. perforans* Leuckart) = Although regarded by some as identical with *C. cuniculi*, this sporozoon is generally held to be distinct because its cysts are smaller, measuring .024-.035 mm. by .0128-.020 mm., and because sporoblastic formation occurs earlier than it does in *C. cuniculi*. It is found most commonly in the intestinal epithelium of the rabbit, in which animal it causes rapid death from severe diarrhoea.

In two human cadavers Eimer found coccidia in the intestinal epithelium. Ralliet and Lucet found coccidia in the faeces of a woman and her child. Rivolta and Grassi have also described coccidia from the stools of children and adults.

*Coccidium baileyi* Stiles 1891. This parasite, found in the intestinal villi of dogs and cats, is distinguished apart from its small size (12.5  $\mu$   $\times$  7-10  $\mu$ ) by the fact that the oocysts are always divided into two masses, each of which encysts and forms spores. According to Blanchard and Braun, the parasite found by Kjellberg is referable to this species and possibly the case described by Grunow (Braun).

*Eimeria hominis*.—Under this name R. Blanchard (1895) described certain bodies which were found by Kunstler and Pitres in fluid aspirated from the chest of a man employed in steamboats trading between Bordeaux and Senegal. The bodies in question were large and contained 10-20 merozoites.

### Conditions that have been described as Psorospermiosis

Peculiar bodies, referred by Rixford and Gilchrist to the protozoa, have been described by these authors under the names *Coccidioides immitis* and *C. pyogenes* (p. 114). The affection in which they were found was first observed by Wernicke and Possadas in Buenos Ayres, and was diagnosed as mycosis fungoides. The parasites were rounded, and measured .003-.03 mm., and were contained in giant-cells which could be seen in the granulation-tissue of the tumour-like masses. Eight similar cases—all fatal—were observed in the United States by Rixford and Gilchrist, Montgomery, Moffit, and Ophüls. In one case there was a chronic nodular skin disease lasting eight years. Nodules were also found in the lung, liver, kidney, genitals, and lymphatic glands. Ophüls considers the protozoon-like parasite to be a pathogenetic fungus.

In a number of other diseases "bodies" have been found which have been variously interpreted as psorosperms, coccidia, or as cell-degenerations; but in recent years the last view has met with most acceptance. Oval "parasites" found in epithelioma contagiosum of fowls and molluscum contagiosum of man have been shewn to have no causal relation to these diseases since Sticker and Marx and Juliusberg found that the infectious agents of these diseases pass through bacterial filters. Psorosperms have also been described in Paget's disease of the nipple by Wickham, Darier, and others, and in psorospermiosis follicularis vegetans or Darier's disease. Darier himself, however, has withdrawn the interpretation he formerly placed upon the bodies in question, and the name of psorospermiosis for these conditions must be regarded as a misnomer, as it is now universally accepted that the so-called "parasites" are cell-degenerations only. [For a discussion on the so-called coccidia of cancer, see Vol. I. p. 625.]

*Ureteritis cystica*.—In chronic inflammatory conditions of the pelvis of the kidney a cystic condition of the ureters may develop (Rayer, Rokitansky, Civiale). The cysts, which vary in size, may contain a watery or colloid material, in which are found round or oval bodies varying considerably in size. The exact nature of these bodies is not known, for whereas Eve, Pisenti, and Bland-Sutton regarded them as coccidia, and v. Kahlden referred them to the myxosporidia, Lubarsch, Aschoff, and most recent writers consider them to be cell-degenerations which have taken place in epithelial masses (v. Brunn's epithelial nests) which occur in the normal ureter.

The exact diagnosis of coccidia is not always easy, and mistakes have been frequently made by those who have no special knowledge of proto-

zoology. The most frequent errors have been in regarding degenerated cells as psorosperms or in mistaking the ova of trematodes for them as in a preliminary communication published by Drs. Finlayson and Catto, the "coccidia" there described being ultimately shewn by Catto to be the ova of a new trematode (*Schistosomum japonicum* or *S. catto*). Commenting on this mistake, the eminent helminthologist Looss remarks somewhat severely but significantly that "it is not the first time that trematode ova have been mistaken for coccidia and it will probably not be the last."

**Sarcosporidiosis.** As Miescher's tubes (p. 103) in the mouse and Rainey's corpuscles in the pig, sarcosporidia infect the voluntary muscles of the lower animals in the form of elongated tube-like bodies filled with sporozoites.

Cases of sarcosporidiosis in man are extremely rare. Apart from doubtful cases by Lindemann and by Rosenberg, a genuine case was first observed by Koch in Egypt. In the same locality Kartulis found them in the muscles of a Sudanese, dead from multiple abscesses of the liver and muscles. Another undoubted case has been reported by Barnard and St. Remy in the muscular fibres of the vocal cords, the parasitic tubes being filled with numerous pseudonavicellæ. The parasite was probably *Sarcocystis lindemanni* Rivolta. Vuillemin has also reported a genuine case caused by *Sarcocystis tenella* Railliet.

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## PARASITIC WORMS

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Bilharziasis, by F. M. SANDWITH, M.D., F.R.C.P.

THE great majority of the larger entozoa, for the most part visible to the naked eye, which infest mankind belong to the two phyla, Platyhelminthes and Nematoda, but the groups Acanthocephala, Pentastomida, and Hirudinea are also represented.

**Platyhelminthes** or Flat-worms have leaf-like or band-like bilaterally symmetrical bodies, either without alimentary canal or mouth, or with a mouth and intestine, which is usually forked. There is no body-cavity and the body is solid. No circulatory or specialised breathing organs exist. The excretory organs are of the so-called water vascular type. Hooks and suckers are often present. The Platyhelminthes are—with rare exceptions—bisexual; the generative organs are complex, a distinct ovary (or germarium) and yolk-gland (or vitellarium) are found. The male and female reproductive pores are usually close behind one another, often in a common genital sinus. The reproduction is usually sexual, but may be complicated by budding.

**Nemathelminthes** or Round-worms are mostly thread- or spindle-shaped. They vary greatly in size, and are covered by a thick cuticle which is sometimes ringed. The mouth is terminal, the anus sub-terminal, the alimentary canal is straight. No specialised circulatory or respiratory systems exist, but the spacious body-cavity contains a corpusculated fluid. The chief nerve-cords, which arise from a circumoral ring, run dorsally and ventrally. The muscles which largely compose the body-wall, the excretory system of two long tubes uniting to open at a common, anterior pore, and the epidermis are all characteristic. The males usually have their tail curled round or are provided with a genital bursa or bell. The vas deferens opens with the anus; the oviduct opens on the ventral side often about one-third the body length from the anterior end. Reproduction is always sexual, but the individuals may be bisexual, hermaphrodite, or parthenogenetic.

Of the **Platyhelminthes** two classes are found parasitic in man—1st, CESTODA, or tapeworms; 2nd, TREMATODA, or flukes. Of the **Nemathelminthes** only one class is at all common, namely, NEMATODA, or thread-worms, but the ACANTHOCEPHALA are represented.

The following list of species, arranged in accordance with this classification, embraces all the more important and well-authenticated worms which, up to the present, have been found parasitic in man :—

## WORMS

(Arranged alphabetically under their Families)

### PLATYHELMINTHES.

#### Cestoda.

*Family*—DIBOTHRIOCEPHALIDÆ.

*Dibothriocephalus cordatus* (p. 847).

*Dibothriocephalus latus* (p. 845).

*Diplogonoporus grandis* (p. 849).

*Pleroceroïdes prolifer* (p. 849).

*Sparganum mansonii* (p. 847).

*Family*—TÆNIIDÆ.

*Davainea madagascariensis* (p. 844).

*Dipylidium caninum* (p. 844).

*Hymenolepis diminuta* (p. 843).

*Hymenolepis lanceolata* (p. 843).

*Hymenolepis nana* (p. 842).

*Tænia africana* (p. 841).

*Tænia confusa* (p. 842).

*Tænia ochinococcus* (p. 976).

*Tænia saginata* (p. 834).

*Tænia solium* (p. 837).

#### Trematoda.

*Family*—FASCIOLIDÆ.

*Cotylogonimus heterophyes* (p. 859).

*Dicrocoelium lanceatum* (p. 856).

*Fasciola hepatica* (p. 853).

*Fasciolopsis buski* (p. 855).

*Fasciolopsis rathouisi* (p. 856).

*Opisthorchis felinus* (p. 859).

*Opisthorchis noverca* (p. 857).

*Opisthorchis sinensis* (p. 858).

*Paragonimus westermani* (p. 860).

*Family*—PARAMPHISTOMIDÆ.

*Cladorchis watsoni* (p. 862).

*Gastrodiscus hominis* (p. 862).

*Family*—SCHISTOSOMIDÆ.

*Schistosomum hematobium* (p. 863).

*Schistosomum japonicum* (p. 851).

### NEMATHELMINTHES.

#### Nematoda.

*Family*—ANGIOSTOMIDÆ.

*Strongyloides stercoralis* (p. 952).

*Family*—ANGUILLULIDÆ.

*Rhabditis niellyi* (p. 919).

*Rhabditis pellio* (p. 920).

*Family*—ASCARIDÆ.

*Ascaris canis* (p. 889).

*Ascaris lumbricoides* (p. 885).

### NEMATHELMINTHES—continued

#### Nematoda.

*Family*—ASCARIDÆ.

*Ascaris maritima* (p. 890).

*Oxyuris vermicularis* (p. 890).

*Family*—FILARIDÆ.

*Filaria bancrofti* (p. 933).

*Filaria conjunctivæ* (p. 920).

*Filaria demarquayi* (p. 951).

*Filaria equina* (p. 921).

*Filaria hominis oris* (p. 921).

*Filaria kilimariæ* (p. 921).

*Filaria labialis* (p. 921).

*Filaria loa* (p. 929).

*Filaria magalhæsi* (p. 951).

*Filaria medinensis* (p. 921).

*Filaria oculi humani* (p. 921).

*Filaria perstans* (p. 932).

*Filaria powelli* (p. 952).

*Filaria restiformis* (p. 921).

*Filaria romanorum orientalis* (p. 921).

*Filaria volvulus* (p. 952).

*Family*—GNATHOSTOMIDÆ.

*Gnathostoma siamense* (p. 955).

*Family*—STRONGYLIDÆ.

*Ankylostoma duodenale* (p. 895).

*Eustrongylus gigas* (p. 893).

*Necator americanus* (p. 899).

*(Esophagostomum) brumpti* (p. 900).

*Strongylus apri* (p. 894).

*Strongylus subtilis* (p. 894).

*Triodontophorus deminutus* (p. 905).

*Family*—TRICHOTRACHELIDÆ.

*Trichocephalus trichiurus* (p. 909).

*Trichinella spiralis* (p. 909).

#### Acanthocephala.

*Echinorhynchus hominis* (p. 957).

*Echinorhynchus moniliformis* (p. 957).

*Gigantorhynchus gigas* (p. 957).

#### Pentastomida.

*Family*—LINGUATULIDÆ.

*Linguatula rhinaria* (p. 958).

*Family*—POROCEPHALIDÆ.

*Porocephalus constrictus* (p. 958).

#### Hirudinea.

*Hæmalipsa ceylonica* (p. 959).

*Limnatis nilotica* (p. 959).

In the following pages all the important Platyhelminthine and Nemathelminthine parasites of man are mentioned. Certain doubtful cases such as *Tænia serrata* (Goeze), *Duvainea* (?) *asiatica* (v. Lin.), or *Filaria immitis* (Leidy), *F. gigas* and *F. ozzardi* (Manson), have been omitted, as the evidence is at present insufficient to justify their inclusion, but with these exceptions our list is complete. Many forms are included which have only been recorded once or twice, and about which very little is known, but it is precisely about these forms that we want more information, and they are worth drawing attention to for this reason alone. Within the limits of this work it is impossible to go deeply into anatomical detail, but more can be found in the systematic treatises on the subject, among which may be mentioned, "Die thierischen Parasiten des Menschen," by Max Braun, Würzburg, 1903<sup>1</sup>; and "Von Würmern und Anthropoden hervorgerufene Erkrankungen," by A. Looss in the *Handbuch der Tropenkrankheiten*, Band i. Leipzig, 1905. The names of others will be found in the list of references. We mention these two as we have used them largely both for synonymy and for the bibliography.

## PHYLUM I.—Platyhelminthes

### CLASS I.—CESTODA

The cestodes or tapeworms are long, flat, white, ribbon-like organisms which, in their mature form, inhabit the alimentary canal of most vertebrates.

Each worm, anatomically speaking, is divisible into a head and neck—*scolex*—and, springing from the latter, a single file of joints or segments—*proglottides*; together these constitute the body or *strobila*. The head is usually provided with two or four strong muscular discs or *suckers*, and, in many species, arranged around a beak or *rostellum*, one or more circles of chitinous *hooklets*. These, the suckers and hooklets, serve to attach the parasite to the mucous membrane of the alimentary canal of the host.

The head is minute, being, as a rule, just discernible with the naked eye at the free end of the narrowest or foremost part of the worm. Tracing backwards from the head or scolex, and originating usually from its posterior part by a process of serial budding, we first come to minute immature proglottides. As we proceed backwards the proglottides become more distinctly differentiated, increase in size, and shew more and more evidences of progress towards maturity. Finally, about half way along the body and long before we arrive at the last elements of the chain, we find that the proglottides are sexually mature, each proglottis possessing elaborate male and female organs of reproduction. Fertilisation takes place between these mature proglottides, and the uterus soon becomes packed with eggs, which speedily secrete an egg-shell and

<sup>1</sup> English translation. London: John Bale, Sons, and Danielsson, Ltd., 1906.

develop into minute embryos. A tapeworm may, therefore, be regarded as a colony, and each individual proglottis as an animal complete in itself. or it may be looked on as a segmented animal, each proglottis representing a single and largely independent segment.

The proglottides contain no organs of digestion, nutrition being effected by absorption from the alimentary juices of the host. Excretion is carried on by an elaborate water vascular system.

The male organs of generation consist of testis, vas deferens, and cirrus (penis); the female of ovary, yolk-gland, shell-gland, uterine receptaculum seminis, and vagina. The vagina and vas deferens usually

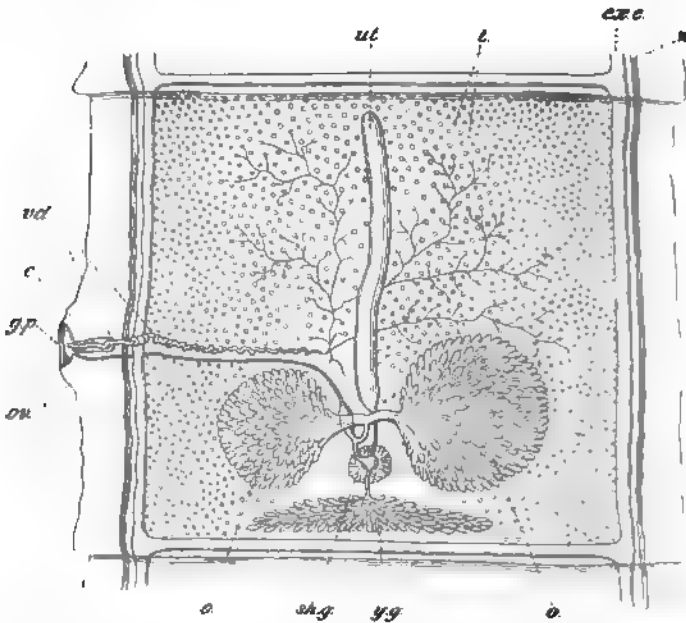


FIG. 116.—Diagram of the reproductive organs of *T. saginata*. c, cirrus bulb; ex.c., excretory canal; g.p., genital pore; n., lateral nerve-cord; o., ovary; o.d., oviduct; sh.g., shell-gland; l., lateral nerve; ut., uterus; v.d., vas deferens; y.g., yolk-glands. From Leuckart and Nitsche.

open into a common genital sinus, which, in its turn, opens externally either on the ventral surface, or laterally usually alternating on the right or left margin of the proglottides (Fig. 116). In some species the male and female genital pores are separated.

When the ova have arrived at maturity the proglottides containing them break off in ones or twos, or in strings, and pass out of the body of the host either by their own proper movements or, more usually, are expelled with the faeces. They are easily recognised as white, oblong, or square bodies which indulge in movements more or less active. The ova they contain are either expelled through a special pore or escape on the decay or rupture of the proglottides, or they may not be set free until the proglottides are swallowed and digested by some animal.

As a rule, in most species at this stage, the egg has developed into the embryo—now enclosed in a thick shell of its own, the yolk having been absorbed at an earlier stage of intra-uterine life. In a few species at the time of its birth the embryo is still undeveloped. In the former the differentiated embryos are ready to enter the body of their intermediate host; in the latter, before they reach this stage, the ova have to pass a certain time in water or in some other medium during which the embryo is developing in preparation for this migration.

The embryo of the cestodes, called an *Onchosphere*, is provided with six hooklets (hence the term “six-hooked embryo” or “hexacanth”) arranged in pairs at one pole of its spherical body. On arrival in the alimentary canal of its intermediate host, the shell in which the embryo is enclosed is dissolved, or in other cases the mantle of cilia with which it

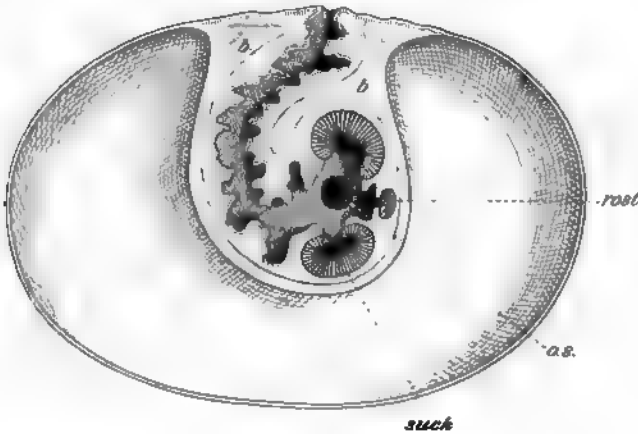


FIG. 117.—*Cysticercus* of *T. saginata*, cut in half to show the invaginated head. *a*, lumen of cyst; *b*, tissue at base of the scolex; *o.s.*, opening of one of the suckers; *rost.*, rostellum; *suck*, suckers. From Leuckart and Nitsche.

is invested is cast. By means of the hooklets it then works and bores its way through the walls of the gut and the intervening tissues until it arrives at the liver, lungs, muscles, brain, connective or other appropriate tissue. The six hooklets are now discarded, and from the pole opposite to that occupied by these hooklets, and by a process differing in detail according to species, a head and neck (scolex), exactly similar to that of the tapeworm from which the embryo originally emanated, is developed.

When this stage is completed it is found that the scolex is inverted within a large, clear, watery bladder,—really the dropsical body of the embryo; from which, when the circumstances are favourable, it can be protruded. This is called a *cysticercus*, and tapeworms so characterised are classified as *cystici*. In another set of tapeworms this cyst is exceedingly minute and rudimentary; such are classified as *cystoulæi*. In a third set the embryo becomes enormously distended by a clear watery fluid; by a sort of budding process from the inner cellular layer of the wall of the

cyst containing this fluid a number of subsidiary *brood-capsules* are formed, the inner layer of which gives origin to tapeworm scolices. These cysts are designated *echinococci*. Yet a fourth type of development is supplied by the *Dibothriocephalidæ*. In them no cyst of any description is formed; the embryo or *plerocercoid*, as it is called, simply enlarges and elongates, the head with two suckorial grooves being formed at one end. In these worms the immature parasite may attain considerable length in the intermediate host—several inches perhaps—and resemble in many respects the mature tapeworm, but they are never sexually mature.

Many cestodes at this stage of development retain for years their capacity for further advance if transferred to the stomach of the definitive host; others again die at a comparatively early date, becoming withered and calcified. On transference to the definitive host the cystic structure is digested off, and the scolex, by means of hooks and suckers, anchors itself to the mucous membrane of the small intestine and rapidly grows into a mature tapeworm.

The **Cestoda** are represented in man by two families, the *Tæniidæ* and the *Dibothriocephalidæ*. The former have four suckers, and usually a single or double row of hooklets on a rostellum. In them the sexual opening is marginal. In the young stage they are *Cysticerci*. The *Dibothriocephalidæ* have no hooks, and only two slit-like suckers, and, as a rule, their sexual organs open on the surface of the proglottides. As already explained, in their immature stage they produce no cyst, but lie free or lightly encysted in the tissues of the intermediate host as *plerocercoid* larvæ.

Practically we have to deal with only three species of tapeworm as adult inhabitants of the human alimentary canal: *Tænia saginata*, or the beef-tapeworm; *Tænia solium*, or the pork-tapeworm; and *Dibothriocephalus latus*, or the fish-tapeworm. The much more serious larval forms of the *Tænia echinococcus* are dealt with in the article on "Hydatid Disease" (p. 976). Besides these a number of other cestodes have been met with in man; and, doubtless, as our acquaintance with the helminthology of savage and semi-civilised peoples extends, yet others will be added to the list.

#### Family I. *Tæniidæ*

i. *Tænia saginata* (Goeze), 1782.—(Synonyms: *T. solium* L. 1767 (pro parte), *T. cucurbitina* Pallas 1781 (pro parte), *T. inermis* Brera 1802, Moquin-Tandon 1860, *T. dentata* Nicolai 1830, *T. lata* Pruner 1847, *Bothriocephalus tropicus* Schmidtmüller 1847, *T. mediocanellata* Küchenmeister 1855, *T. zittaviensis* Küchenmeister 1855, *T. tropica* Moquin-Tandon 1860, *T. (Cystotænia) mediocanellata* Leuckart 1863) (Fig. 120).—*T. saginata* in the adult state lives exclusively in the alimentary canal of man. This is one of the commonest and most widely distributed of the human tapeworms. According as it is elongated or contracted, it measures



from 4 to 8 metres in length,<sup>1</sup> and is composed of from 1200 to 1300 proglottides. The more mature proglottides are long (16-20 mm., and 3-7 mm. broad); those about the middle of the worm are broad (12-14 mm.); those constituting the more immature portion gradually taper in size to very narrow and extremely delicate dimensions. The pear-shaped head (Fig. 121, A and B) (1.5-2 mm.) is provided with four powerful suckers, but has neither hooklets nor rostellum. The marginal genital pore projects markedly, and leads to a uterus having many—twenty to thirty-five—lateral dichotomously dividing branches. The contained eggs, or rather shelled embryos, are minute (0.03 to 0.04 by 0.02 to 0.03 mm.), slightly oval bodies. The shell is thick and encloses a six-hooked embryo.

Carefully conducted feeding experiments have conclusively proved that the ox acts the part of intermediate host to *T. saginata*. The cystic stage of the parasite known as *Cysticercus bovis* (7.5 to 9 mm. × 5.5 mm.) is passed in the muscles of this animal; more rarely in the liver and other viscera. It is not known how long the cysticerci retain their vitality, several years probably, before becoming shrivelled and undergoing calcareous changes; but it is known that when man consumes raw or imperfectly cooked beef containing living cysticerci, *T. saginata* is developed in his intestine.

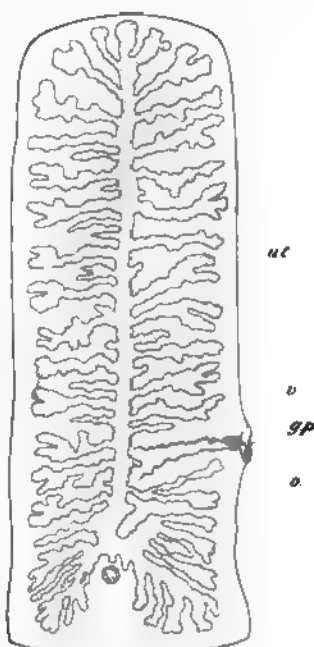


FIG. 118.—Ripe proglottis of *T. saginata* (magnified). g.p., genital pore; v, oviduct degenerating; ut, uterus; r, vas deferens degenerating. From Leuckart and Nitsche.



FIG. 119.—Egg of *Tenias saginata* (× about 400). Brown in colour. From Looss.<sup>2</sup>

Thus it comes about that in countries in which much and imperfectly cooked beef is eaten this tapeworm is very prevalent; more particularly is this the case where the cattle are badly fed and tended, and where they are therefore in their turn much exposed to infection by tapeworm ova. Comparatively rare in Western Europe and the United States of America, *T. saginata* is common in Eastern Europe, in Asia, Africa, and parts of South America. In many districts it is excessively common. In Abyssinia, for example,

<sup>1</sup> Béranger-Féraud records a specimen which attained a length of 74 metres! In this and in similar instances of apparently abnormally long tapeworms, the fragments of several individuals have been regarded as belonging to one animal.

<sup>2</sup> The figures of ova described as from Looss in this article are all magnified to the same extent, about 400 times, and thus shew the relative size of the eggs found in human faeces.

nearly every native entertains one or more of these unpleasant guests. In the North-West Provinces of India, where about 5 per cent of the cattle are affected with cysticerci, it is nearly as prevalent,—a condition entirely attributable to the filthy habits of the people, their carelessness in the management of their cattle and in the cooking of their food.

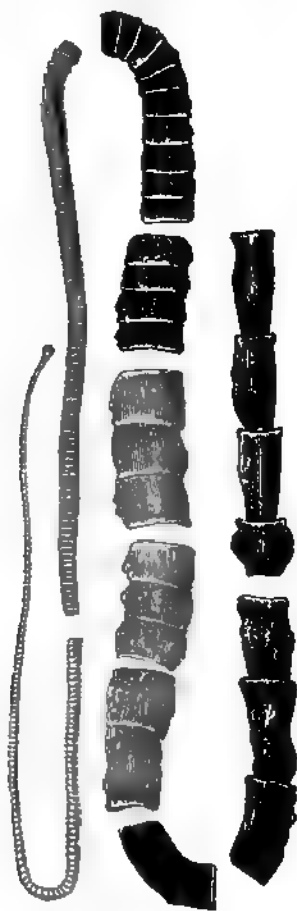


FIG. 120.—*T. saginata* (nat. size).  
After Leuckart.

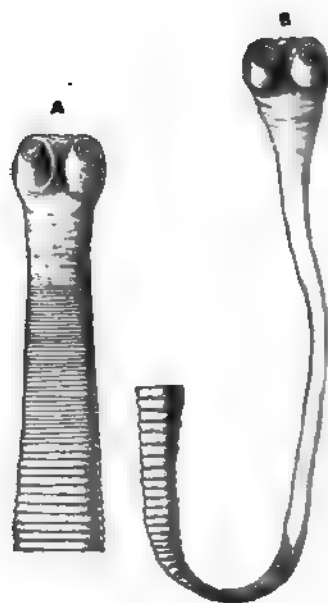


FIG. 121.—Head of *T. saginata*. A, contracted.  
B, extended ( $\times 8$ ). After Leuckart.

and their personal uncleanness. Of late years this tapeworm is said to be becoming more common in the south of France in consequence of the large importation of Algerian bullocks.

Measly beef (Fig. 122), that is, beef affected with *Cysticercus bovis*, is easily recognised. Here and there, scattered throughout the muscles and lying lengthwise between the fibres are to be seen small, oblong

watery cysts, measuring 7.5 to 9 mm. by 5.5 mm. If one of these cysts is shelled out and examined with a lens, the invaginated head of the immature cestode can be detected in its inside. By placing the cyst in warm salt solution the head becomes evaginated (Fig. 123), and is seen to be attached to the end of a long neck springing from the short equator of the cyst. Under the microscope the four suckers and unarmed head of *Tænia saginata* are readily recognised.

*Cysticercus bovis*, unlike the cysticercus (*C. cellulose*) of *T. solium*, is very rare in man. The only animals besides the ox in which it has hitherto been found are the goat and the giraffe. Attempts to rear the tapeworm in the dog have failed. It is said to live for some eight months in the ox at least before it begins to undergo calcareous degeneration. A temperature of 47° or 48° C. always kills it.

It has been proved that from the time the cysticercus is swallowed to the appearance of proglottides in the stools about sixty days must elapse. At the end of this time eight or twelve or more proglottides are thrown

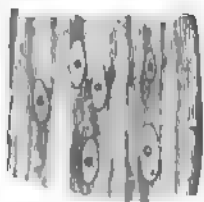


FIG. 122.—*Cysticercus* of *T. saginata* or *Cysticercus bovis* in beef (nat. size). After Leuckart.



FIG. 123. *Cysticercus bovis*: head evaginated ( $\times 8$ ). After Leuckart.

off daily by the now mature worm during an indefinite number of years. The proglottides rarely appear in the stools in strings, as with many other tapeworms; they are usually given off singly, sometimes passing out of the bowel independently of the act of defecation and by their own proper locomotive activity. Thus, besides being nearly a constant feature in the stools, they may creep out of the body, and, as a consequence, are frequently found in the patient's clothes, in his bed, or about his room. During their wanderings the remarkable elongations and shortenings and muscular contractions of the proglottides bring about the expulsion of the eggs—very commonly from a rupture in the fore part of the uterus. In this way these eggs are strewn about, and, if fortune favour them, are appropriately placed for ingestion by the ox.

A knowledge of the facts of the life-history of this, as of all other parasites, is of extreme importance, as indicating with precision the direction that prophylactic measures should take.

ii. *Tænia solium* L. pro parte 1767.—(Synonyms: *Tænia cucurbitina* Pall. 1781, *T. pellucida* Goeze 1782, *T. vulgaris* Werner 1782, *T. dentata*, Gmel. 1790, *Halysis solium* Zeder 1800, *T. humani armata* Brera 1802, *T. (Cystotenia) solium* Leuck. 1862.)—This tapeworm is

distinguishable from the foregoing by its smaller size, averaging from



FIG. 124.—Head of *T. solium* (x 45).  
After Leuckart.



FIG. 125.—Ripe and half-ripe  
proglottides of *T. solium*  
(nat. size). After Leuckart.

2-3.5 metres in length, but especially by the double circle of twenty-two

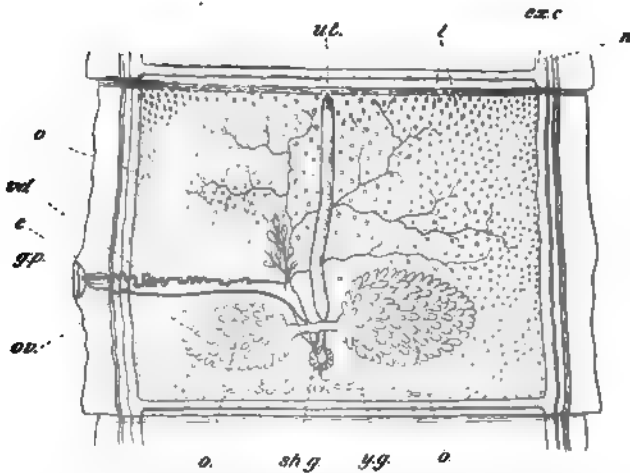


FIG. 126.—Diagram of the reproductive organs of *T. solium*. *c*, cirrus-bulb; *ex.c.*, excretory canal; *a.p.*, genital pore; *a*, lateral nerve; *ov*, ovary; the third anterior lobe serves to distinguish this species from *T. saginata*; *ov*, oviduct; *sh.g.*, shell-gland; *t*, testes; *ut*, uterus; *c.d.*, vas deferens; *g.g.*, yolk-glands. From Leuckart and Nitsche.



FIG. 127.—Ripe proglottid of *T. solium*. *g.p.*, genital remains of oviduct; *c*, remains of vas. From Leuckart and

to thirty-two, usually twenty-six to twenty-eight, hooklets which surround the medium-sized rostellum (Fig. 124). The spherical head (0

to 1.0 mm.) carries four large somewhat prominent suckers. The neck is thread-like, the segments very gradually increasing in size up to about the middle of the worm, where they measure rather under 8 mm. in breadth. The proglottides number 800 to 900. Towards the free end the ripe proglottides (Fig. 125) elongate and become narrower, measuring there from 10 to 12 mm. in length by 5 to 6 mm. in breadth. The genital pore is marginal and more or less regularly alternate. The uterus has on each side seven to ten lateral branches, which divide dendritically. The eggs, or rather embryos, are spherical (0.03 mm.), and have a firm, thick, brownish shell. The worm lives exclusively in the small intestine of man. The proglottides as they become ripe are discharged singly or in chains with the fæces of the host, and in this way the ova, while still in the proglottides, or after expulsion from them during their slow movements, get an opportunity of being transferred to the stomach of the pig or, occasionally, of other animals, including man himself.



FIG. 128.—Egg of *Tania solium* ( $\times$  about 400). Light brown in colour. From Looss.

Arrived in the stomach of a vertebrate, the shell enclosing the six-hooked embryo is dissolved by the gastric juices. Being thus liberated the embryo works its way through the gut and into the viscera, muscles, and connective tissue of the intermediate host. The connective tissue between the muscular fibres seems to be the more normal and usual destination for the embryo, but it may come to rest in almost any organ. In muscle the embryo becomes transformed in the course of a few weeks into a clear, elliptical cyst (usually 8-10 mm. in length), the *Cysticercus cellulosæ*; its long axis is disposed in the direction of the muscular fibres which it separates (Fig. 129). This cyst contains the spirally rolled and much-wrinkled invaginated cestode head which in hooks, suckers, rostellum, and in every other respect resembles the scolex of *Tania solium* (Fig. 130). The parasite may degenerate at an early age, but there is at least one recorded case in which a living cysticercus located in the eye was under observation during twenty years.

Pork beset with these cysticerci—the long and well-known *Cysticercus cellulosæ*—is known as “measly pork.” When eaten raw, or imperfectly cooked, it leads in man to the development of *Tania solium* in the intestine, as has been amply proved by feeding experiments. It is a comparatively rare thing, in Europe at all events, to find more than one *Tania saginata* in the same individual host; hence this tapeworm is sometimes called the *ver solitaire*. It is otherwise with *Tania solium*—two, or many more, being frequently found together.

The geographical distribution of *Tania solium* corresponds with that of the pig; its greater or less abundance in any particular district or country depending on the way the swine are tended, the habits of the natives as regards the disposal of their dejecta, and the way in which they prepare their pork for the table. In 3814 post-mortem examinations in North Germany the mature tapeworm was found about once in

every 200 bodies. In South Germany, in France, in Great Britain, and in the United States, it is by no means so frequent. Naturally the *Cysticercus cellulosæ* has a corresponding geographical distribution. According to Leuckart, in Prussia, in 1,728,600 swine examined in 1876 one carcass in every 370 had *Cysticercus cellulosæ*. As regards man, in 9753 post mortem examinations of human bodies in various Pathological Institutes in North Germany, the cysticercus was found once in every 76 bodies. In 1869 *T. solium* was as common in Denmark as *T. saginati*, now it has almost entirely disappeared, but both species are found there as often in women as in men (Krabbe). In Western Europe their

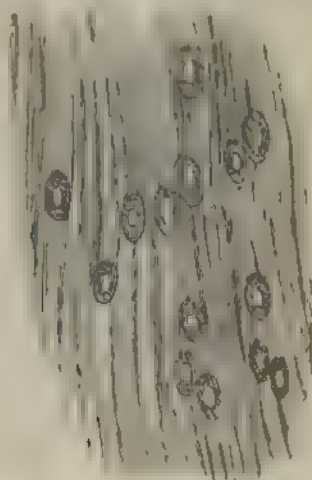


FIG. 129. Cysticercus of *T. solium* in pork (nat. size). After Leuckart.



FIG. 130. Cysticercus of *T. solium* (nat. size). After Leuckart.

occurrence is not nearly so common. The greater frequency of cysticercus in man, as compared with the pig, is of course attributable to the greater care with which they are searched for in the former, and to his greater age—not to his superior susceptibility or greater liability.

In consequence of the liability of man to cysticercus infection through his swallowing the eggs of *T. solium* in food or in water, or from their introduction by soiled hands, or, as some suggest, by a sort of auto-infection from the regurgitation into the stomach of the ripe proglottides of the tapeworm during an act of vomiting, or in other ways, and in consequence of the frequency with which the *Cysticercus cellulosæ* develops in the brain, eye, heart, and other localities (rarely in the liver, never in the bones), it becomes an object of considerable pathological importance. Cases are on record in which hundreds and even thousands of cysticerci were found in the various organs. Such wholesale infection is, however, rare. Strange to say, the parasite seems to have a predilection for the brain and eye, and in not a few instances it has been found restricted to



se organs. In the brain the cysticerci are usually found in the membranes or in the cortex, more rarely in the interior. In eighty-eight cases collected by Küchenmeister they were found forty-nine times in the membranes, thirty-nine times in the cortex, thirty-six times in the great ganglia, nineteen times in the central substance, and eighteen times in the ventricles. Von Graefe calculated that in Berlin ophthalmic practice the cysticercus was observed in the eye once in about every thousand cases. In England they are very much rarer. Their most common position in the eye is beneath the retina; about half as frequently they are found in the vitreous humour; still more rarely they appear in the anterior chamber and elsewhere. In the aqueous and vitreous humours the parasite is free, and the movements of the head and neck can readily be made out. In these cases it is probable that in the first instance the cysticerci were developed behind the retina, or in the iris, and that afterwards they had broken loose.

Cysticerci developed in the arachnoid or pia mater assume, in certain instances, a peculiar branched appearance which has gained for them the name of *Cysticercus racemosus* or *multilocularis*, a name very apt to be understood. In this situation the immature parasite may grow to a great size (8-25 cm.) and have many branches and diverticula. The peculiar form of this variety of cysticercus is probably attributable to the conditions of the pressure under which it grows; conditions which appear to regulate the size and shape of the cyst in the different localities of the body, wheresoever it chances to be located. In the ventricles of the brain it may grow to be as big as a pigeon's egg.

Occasionally the cysticerci develop under the cutis, where they form small tumours the size of a pea. The concurrence of such tumours, or of a cysticercus in the eye with cerebral symptoms, is a valuable point in determining the diagnosis of obscure brain disease.

Unless removed early, cysticerci in the eye ultimately lead to the destruction of the organ, and perhaps to sympathetic inflammation of the other eye. In the heart they may give rise to functional irregularities, even to valvular insufficiency. In the lungs they may produce inflammatory affections. In the brain, particularly when located in the central ganglia, or when they press upon nerve-trunks, motor or sensory tracts, or centres, they may give rise to paralytic or epileptic conditions; when on the surface of the brain they are usually of less moment.

A form once described as *Tænia acanthotrias* is known in the cysticercus stage only, and has only very rarely been met with. It was first described in the muscles, under the skin, and in the brain of a white woman from Virginia, U.S.A. In appearance it resembled the cysticercus of *Tænia solium*. The scolex carried from forty-two to forty-eight hooklets, arranged in a triple circle round the rostellum. It is now usually looked upon as an aberrant form of *Cysticercus cellulosæ*, and therefore a larval form of *T. solium*.

iii. *Tænia africana* v. Linstow 1900. — This tapeworm is about

1.3 m. in length. The proglottides are throughout broader than they are long. The head is unarmed, and the four suckers look forward, the

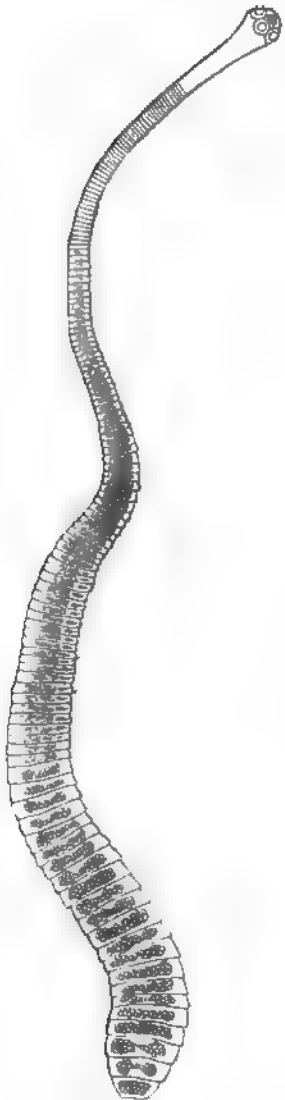


FIG. 11 *Hymenolepis nana* (× 18).  
After Leuckart.

short neck is somewhat broader than the head. The proglottides number about 600, and the last is 7 mm. long by 12 to 15 mm. broad. Genital pore lateral and irregularly alternate. Testes very numerous, and vas deferens much coiled. Ovary paired, large, and with many radiate diverticula. Uterus with 15 to 24 radiating but not branching diverticula. Egg-shell thick, ova 0.0312 by 0.0338 mm. across. Two examples of this worm inhabited a native soldier near Lake Nyassa. The life-history is unknown, but it has been suggested that the cysticercus lives in the zebu (*Bos indicus*), whose flesh is often eaten raw in these districts.

iv. *Tænia confusa* Ward 1896. — The head of this worm, which reaches 8.5 m. in length, is unknown. The proglottides, which are always longer than broad, are 700 to 800 in number; the terminal is 35 mm. long by 4 to 5 mm. broad. The reproductive pore is behind the middle of the segment and irregularly alternate. Testes numerous, but vas deferens not much coiled. Ovary paired, small, each half rather bean-shaped. Uterus with 14 to 18 short unbranched diverticula. Egg-shell thick, radially striped, egg measuring 0.039 by 0.3 mm. Only two examples of this worm are recorded; these were passed by a man in Lincoln, Nebraska. The life-history is quite unknown.

v. *Tænia echinococcus* v. Sieb. 1853. — See art. on "Hydatids" (p. 976).

vi. *Hymenolepis nana* (v. Sieb.) 1852. — (Synonyms: *T. nana* v. Sieb. 1852) (see van Beneden 1867), *T. ægyptiaca* Bilharz 1833, *Diplocanthus nanus* Weindl. 1858, *T. (Hymenolepis) nana* Leuckart 1863) (Fig. 131). — Grassi regards this tapeworm as identical with *Tænia murina* of the rat, but this view is not universally accepted. As a human parasite it was first discovered by Bilharz, in 1851, in the ileum of an Egyptian boy. It is one of the

smallest of the tapeworms infesting man, measuring only from 10 to 15, rarely 20 mm. in length, by 0.5 to 0.7 mm. in breadth. The

spherical head (0.3 mm.) carries four suckers and a very prominent rostellum—often invaginated—surrounded by a single circle of from 24 to 28 or 30 minute hooklets, only 0.014 to 0.018 in length. The joints, which are short and broad, number from 150 to 170; they have a marginal genital pore, and when approaching maturity possess thirty or more ova (0.04 mm.), containing a six-hooked embryo (0.016 to 0.019 mm.) enclosed in two thin, clear, and widely separated, firm egg-shells. So minute a worm has doubtless been many times overlooked. In the instances, now not a few, in which its presence was ascertained it was found in hundreds. Lately cases have been reported from Belgrade, Italy, Russia, England, France, Germany, South America, Siam, Japan, and the United States. Grassi says it is very common in the south of Italy and in Sicily, particularly in children. Its life-history is unknown, but some authorities think the second host is an insect or a myriapod. It exists in great numbers in the intestine (250 to over 1000) and is the cause of disorder of a more serious type than those produced by the larger tapeworms. According to Grassi, the *H. murina* develops direct in the rat without the interposition of an intermediate host.



FIG. 122.—Egg of *Hymenolepis nana* (x about 400). Colourless. From Looss.

vii. *Hymenolepis diminuta* Rud. 1819.—(Synonyms: *Tenia diminuta* Rud. 1819, *Tenia leptocephala* Creplin 1825, *T. flavo-punctata* Weinld. 1858, *T. variegata* Par. 1884, *T. minimus* Grassi 1886.)—The occurrence in man of this tapeworm has been recorded three times in America, rarely in Italy, Denmark, France, and South America, and each time in a child. Only once was the head found. This is like that of *Tenia saginata*, though somewhat smaller (0.2 to 0.5 mm.); it has four elliptical suckers, and is devoid of hooklets and rostellum. The neck is filiform, gradually expanding till at the posterior part of the worm the ripe proglottides—which are trapezoid, sometimes triangular in shape—measure 0.66 mm. in length by 3.5 mm. in breadth, or less. The joints in the fore-part of the worm are marked by a large yellow spot. This spot is the distended receptaculum seminis. Posteriorly this mark disappears, giving place to a brownish-gray colour derived from the crowd of ova filling the uterus. A notable proportion of the proglottides are barren. The eggs (0.06 mm.) possess a smooth, double outline, and enclose a six-hooked embryo surrounded by an oval, striated, and somewhat thickish shell (0.03 mm.). The genital organs open laterally. This tapeworm is normally a parasite of rats and mice, though it occasionally makes its way into infants and children. Its larva, according to Grassi and Rovelli, lives in the larva and adult of a small moth *Asopa firmalis*, in an orthopteron *Anisolabis annulipes*, and in the beetles *Acis spinosa* and *Staurus striatus*.

viii. *Hymenolepis lanceolata* Bloch. 1782.—(Synonyms: *T. lanceolata* Bloch, *Drepanidokentia lanceolata* Railliet 1892.)—This worm is 30 to 130

mm. long, 5 to 18 mm. broad. The head is small with a row of eight hooks, each measuring 0.031 mm. The neck is short. The proglottides are very broad. The normal host is the duck and the goose, and the intermediate host is a *Cyclops*. It has, however, been passed by a boy on two separate occasions at Breslau.

ix. *Davainea madagascariensis* Davaine 1869. — (Synonyms: *D. madagascariensis* Dav., *T. demerariensis* Daniels 1895.) — Our knowledge of this tapeworm is still imperfect. It has been found in Mayotte (one of the Comoro Islands), in Mauritius, in Siam (Bangkok), and in British Guiana. It may attain a length of 25 to 30 cm., and have 500 to 700 proglottides. The terminal proglottides have a breadth of 0.390 mm and a length of 1.055. The head has four suckers and a rostellum armed with about ninety hooklets, 0.018 mm. long. In the interior of the proglottides the eggs are arranged in balls disposed in transverse rows. The genital pores are lateral and on the same side. The intermediate host is unknown, possibly some widely distributed insect such as a cockroach.<sup>1</sup>

x. *Dipylidium caninum* (Linn.) 1758. — (Synonyms: *T. caninum* L. 1758 pro parte, *T. moniliformis* Pallas 1781, *T. cucumerina* Bloch. 1782, *T. elliptica* Batsch 1786, *Dipylidium cucumerinum* Leuck. 1863.) — This is more especially a parasite of the dog and cat; but it occurs not infrequently in man, particularly in Scandinavia. Usually it is found in young children. The mature worm measures from 10 to 40 cm. in length. It has a long, very extensile, thread-like neck which gradually expands into segments, 6 to 7 mm. long by 2 to 3 mm. broad, of a peculiar reddish tint derived from the ova they contain. The small head has four suckers and a stout, rounded rostellum carrying from forty to sixty hooklets set on disc-like bases, and arranged in three or four somewhat irregular rings. The terminal joints, shaped like melon seeds, are much rounded at the corners, and also much elongated — four or five times longer than broad. The sexual organs, with the exception of the uterus, which is single and central, are double, with openings on both margins of the proglottis. In the dog many individuals are found together — sometimes hundreds. To the thirty-six recorded cases of this parasite found in man Zschokke has recently added another. His specimen came from a four-year-old boy in Bâle, who was accustomed to play with dogs.

The dog-flea, the human flea, the dog-louse (*Trichodectes canis*) serve as the intermediate host of this tapeworm. When the cysticercoids have gained the lips and mouth of the dog, they are readily transferred to those human beings who are uncleanly enough to allow dogs to lick them. It is, when found in man, almost exclusively confined to children who play with dogs. Cases have been recorded in all countries in the north of Europe.

<sup>1</sup> I have recently received some proglottides which I take to be of *D. madagascariensis* from Durban. — A. E. S.

## Family II. Dibothriocephalidae

**Bothriocephalus latus** (Linn.).—(Synonyms: *T. lata* L. 1748, *T. l.* 1748, *T. grisea* Pallas 1796, *T. membranacea* Pallas 1781, *T. allas* 1781, *T. dentata* Batsch 1786, *Bothriocephalus latus* Bremser 1850, *Bothrium latum* Dies. 1850, *Bothriocristatus* Davaine 1874, *Bothriobullicus* Küchenmeister 1855, *B.*

Bugn. 1885) (Fig. 133).—This is of considerable size, measuring 10, exceptionally from 12 to 16 metres in length. It is readily shable from the other tapeworms man by this feature, by its great by the relative shortness of the pro- by the brownish rosette-shaped nd by the central position of the penings. The head (Fig. 135)

by 1 mm.) is somewhat flattened, ngated olive shape, and is provided laterally placed sucktorial grooves; ither rostellum nor hooklets. The

fore part are very extensile, being thicker according to the state of on. Traced backwards the segments become broader, till about the of the worm, where they measure mm. in breadth by 4 or 5 mm. in Farther back the segments become and elongate, so that about the they are nearly square. The

of the segments are thin and flat, central portion is thicker, bulged the gravid uterus. The segments

numerous—3000 to 4200 some- In those which are riper the uterus, l with ova, is thrown into radially

folds, forming what is known as rine rosette," under the middle of part of which the sexual openings e found. These openings are two r, and are placed close together,—

rior, a transverse slit in which are cirrus-sheath and vulva, rior, the punctiform opening of the uterus. The eggs are oval 0.071 by 0.045 mm.); the shell is simple, brown, and closed in id by an operculum.

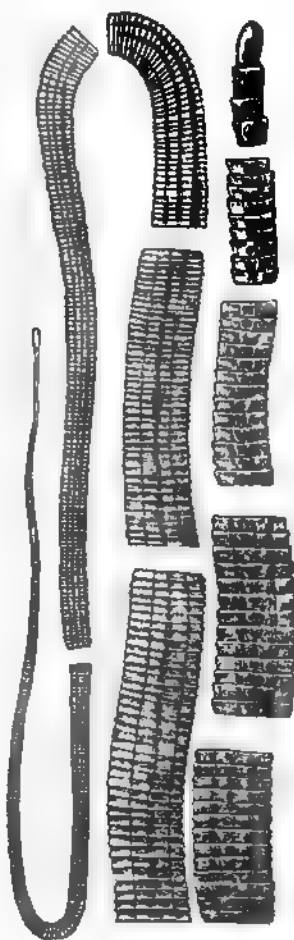


FIG. 133.—*Dibothriocephalus latus* (nat. size). Leuckart.

In the other human tapeworms already described the embryo is formed *in utero*, and very generally the vitelline portion of the ovum has disappeared before the proglottides are detached: the embryo, in fact, enclosed in its own proper shell, is the only part of the ovum remaining. This is not the case in *Dibothriocephalus latus*. While *in utero*, and perhaps for months afterwards, the embryo is still undeveloped, and the egg retains all the characters of an undeveloped ovum. To secure maturation of the ovum it has to lie in water for a longer or shorter time, according to temperature and other circumstances. A ciliated



FIG. 134.—Egg of *Dibothriocephalus latus* ( $\times$  about 400). Dull brown colour. From Looss.

six-hooked onchosphere is then developed which, when sufficiently mature, effects its escape from the egg-shell by forcing back the operculum; it then swims about in the water like an infusorian. This ciliated swimming form gains access, either directly, or possibly through the body of another animal as yet unrecognised, to certain fishes, particularly pike, burbot (*Lota vulgaris*), members of the Salmonidae, and other fresh-water species, which act as intermediate hosts to the young parasite. In these fishes young *Dibothriocephali* are often found in large numbers lying free or only feebly encysted in the viscera and muscles (Fig. 136). They are not destroyed

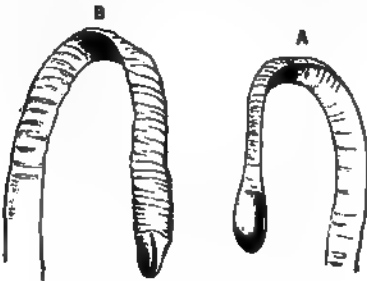


FIG. 135.—Head of *Dibothriocephalus latus* ( $\times$  8). A, from the flat side; B, from the margin. Leuckart.



FIG. 136. Larvæ of *Dibothriocephalus latus* from the pike. A and B with extended, C with retracted head. (A, nat. size; B and C,  $\times$  2.) Leuckart.

by salting, pickling, or smoking. They have no caudal cyst, nor do they exhibit any indication of having gone through such a metamorphosis as takes place in the higher cestodes; the embryo seems simply to lose its mantle of cilia, to drop its six hooklets, and then to elongate itself, the future suckers becoming visible as depressions or slits at one end of the larva. The head and tail are usually found invaginated. The young worm grows to 1 or 2.5 cm. in length by 2 or 3 mm. in breadth. In this condition it is transferred in raw, smoked, or imperfectly cured or cooked fish to the intestine of man, dog, cat, or other ichthyophagous animal, where it rapidly develops into the mature *Dibothriocephalus latus*.

In these facts, which have been proved many times by experiment



we have the explanation of the peculiar and narrowly limited geographical distribution of this parasite, which, so far as we know, is confined to the shores of the Franco-Swiss lakes, to Northern Italy, to Bavaria, the eastern and western shores of the Baltic, Poland, Turkestan, and Japan. A few cases are reported from Ireland and the United States. In some of these countries a very large proportion of the inhabitants are affected; in St. Petersburg, it is said, 15 per cent. As the individual parasites may live a very long time, up to twenty-one years even, and as the fish containing the larval *Dibothriocephali* are frequently exported and consumed in countries outside the strictly endemic areas, *Dibothriocephalus*

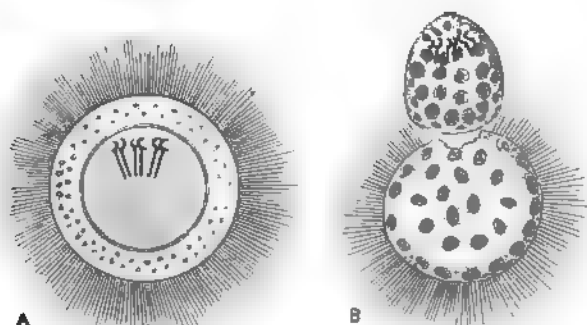


FIG. 137.—A, Free-swimming, six-hooked larva of *Dibothriocephalus latus* (the broad tapeworm of Man), still enclosed in a ciliated membrane or mantle. In this condition it may continue to live in water for a week or more, but eventually throws off its ciliated coat (as in B) and commences to creep about vigorously by the aid of its hooks, in search of its first host, which is at present unknown.  $\times 600$ . After Schaubinsland.

*latus* is sometimes met with at a distance from its usual and endemic haunts.

ii. *Dibothriocephalus cordatus* (R. Leuck.) 1863.—(Synonym: *Bothriocephalus cordatus* Leuck.)—Hitherto this worm has been found in man only rarely. It occurs in Greenland and Iceland, where it appears to be common enough in dogs, seals, and walruses, and where, doubtless, its occurrence is dependent on the ichthyophagous habits of men and beasts. It measures about 80 to 115 cm. in length, the terminal joints being about 5 mm. square. The head (2 mm.) is described as being short, broad, and cordiform, with lateral wings having at their borders a longitudinally placed groove or sucker. The segments attain their maximum breadth, and also reach sexual maturity, at a very short distance (3 cm.) behind the head. From the shortness of the neck the anterior end of the worm is lancet-shaped. The genital organs open ventrally.

iii. *Sparganum mansoni*<sup>1</sup> (Cobbold) 1883.—(Synonyms: *Ligula mansoni* Cobbold 1883, *Bothriocephalus liguloides* R. Leuck. 1886, *Dibothrium mansoni* Ariola 1900.)—This is the larval form of an

<sup>1</sup> Stiles suggests this name since the larva is not in the narrowest sense a *Ligula* or a *Bothriocephalus*.

unknown species of the Dibothriocephalidæ. In making a post-mortem examination of a Chinese, in Amoy, a number of specimens of this parasite were found under the peritoneum in the neighborhood of the kidneys and iliac fossæ, and also one apparently free specimen in the pleural cavity. They were more or less coiled up and irregularly disposed in the sub-peritoneal fascia, and looked like ribbon-strings of pale fat underneath the serous membrane. On being turned out they were found to be long, white, ribbon-shaped parasites, with feeble yet distinct movements. No differentiated head, no definite structure, and no evidence of sexual organs were discovered, neither was there any attempt at segmentation. When fresh the parasites measured about 30 to 35 cm. in length, by about

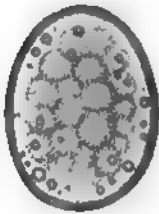


FIG. 138.—Egg of *Diplogonoporus grandis* ( $\times$  about 400). Light yellow brown in colour. From Looss.

3-12 mm. in breadth. They tapered slightly towards one end; at the broad end there was a sort of papilla which in some instances was



FIG. 139.—Various forms of *Pterocercoides prolifer* ( $\times 4$ ). From Iijima.

retracted. Scheube extracted a similar parasite from the urethra of a Japanese.

Leuckart suggests that the host of the mature form of this parasite is a carnivorous animal closely associated with man. Sonsino found a similar, if not the same, parasite in an Egyptian jackal.

iv. *Diplogonoporus grandis* (R. Blanch.) 1894.—The head of this worm is unknown, but portions of body 10 m. long have been passed in Japan. The proglottides are broad, from 14 to 16 mm. to 25 mm., with two parallel lines of black spots. The eggs are oval, 0·063 by 0·048 to 0·05, with opercula.

v. *Plerocercoides prolifer* Ijima 1905.—(Synonyms: *Bothriocephalus* sp. Ijima and Kurimoto 1894, *Krabbea grandis* R. Blanch.) This is the name given by Ijima to a plerocercoid larva he has recently described from the subcutaneous tissues of a Japanese woman. Like the *Sparganum mansonii*, it is only known in the larval state, and until we know the parent form it will be impossible to name it accurately. Vast numbers of the parasite were found encapsuled in the subcutaneous and neighbouring tissues. Ijima calculated that there were 10,000 larvæ in the left thigh alone. Others were found free. The parasites multiply by transverse fission and by budding. There seem to be no hollow slits or side-suckers. This form is possibly identical with *S. mansonii*.

#### SYMPTOMS PRODUCED BY TAPEWORMS

In many instances of tapeworm infection the parasite appears to give rise to no inconvenience whatever, its presence being entirely overlooked, or only made known by the appearance of proglottides—singly or in chains—in the stools. Usually, however, there is complaint of colicky pains in the abdomen, perhaps of alternating diarrhoea and constipation. Nausea and other dyspeptic sensations are often complained of, particularly when the patient is fasting. In a certain proportion of cases the general nutrition suffers, or a state of anæmia may appear and be regarded as pernicious.

In not a few cases grave nervous disturbances—such as giddiness, epileptiform seizures, chorea, hallucinations, and other neuroses—have been attributed to these parasites, and apparently with justice; at all events, it is stated that such symptoms disappeared on the expulsion of the presumed cause. As can readily be understood, the hypochondriacal temperament is apt to dwell on such a subject, to exaggerate actual symptoms, to imagine others, and to persist in the belief that a worm is present either where no worm had ever existed, or after its complete expulsion—a sort of tæniaphobia.

The blood in these cases usually shews but little change from the normal. In a few cases of *Tænia* infection, however, the eosinophil leucocytes are markedly increased in numbers—Leichtenstern records a count of 34 per cent, Limasset one of 26 per cent, whilst several other authors have noted over 10 per cent eosinophils in some of their cases. Limasset, who carefully studied the blood changes in sixteen cases of tapeworm infection, found that five of these at some period shewed more

than 5 per cent eosinophils, and two at some period more than 10 per cent. *Cysticercus* cysts may also set up in the blood a typical eosinophilia of over 10 per cent. *Dibothriocephalus latus* rarely affects the blood leucocytes; in some cases, however, it seems to have been the cause of a relative increase in the eosinophil cells. The profound anæmia to which it occasionally gives rise closely simulates "primary pernicious anæmia" characterised by the presence in the blood of nucleated red blood-corpuscles, the majority of which conform to the megaloblastic type, by the presence of poikilocytes and of cells shewing polychromatophilia.<sup>1</sup>

It is said that *Dibothriocephalus latus*—on account, probably, of its greater size—is apt to be accompanied by more marked symptoms (more especially profound anæmia—"bothriocephalus anæmia")—than either *T. saginata* or *T. solium*. *Hymenolepis nana* and *Davainea madagascariensis*—particularly the latter—are credited with causing nervous symptoms of unusual severity; probably because they occur principally in children.

For the diagnosis of species from the proglottides passed by the patient the reader is referred to the descriptions already given of the various tapeworms.

**Treatment.**—The number of drugs which have been employed as tæniafuges is very great. Most of these are now discarded. The male fern, pomegranate root bark and its alkaloid pelletierine, koussou or cusso, pumpkin seeds, and turpentine are, in about the order stated, those most generally employed at the present day. The exact value of thymol and eucalyptus oil as tæniafuges has yet to be determined; but as these drugs frequently procure the expulsion of tapeworms, ascarides, and distomes when given in cases of ankylostomiasis, they promise to be valuable additions to the pharmacopœia as efficient, all-round anthelmintics.

Before administering any of these drugs it is always desirable to secure an empty condition of the bowel—preferably by salines, which clear away any mucus which may protect the worm—and it is always well to follow up their administration by a smart cathartic. The anthelmintic does not as a rule kill the parasite, but only paralyses it, from which state of paralysis, if not quickly swept out of the intestine, it would probably recover in a short time and renew its hold, temporarily relaxed, on the mucous membrane. As most of these drugs exercise to a certain extent a toxic effect on the host, as well as on the parasite, it is always well for the patient to lie down for an hour or two, or until these toxic effects have passed away. Good rules are:—a cupful of milk instead of the usual full evening meal; early next morning the tæniafuge on an empty stomach; shortly afterwards a brisk cathartic, the recumbent position being maintained until the latter has acted; in the event of part of a tapeworm protruding at the anus it must not be pulled, lest it snap across, and the head, remaining behind, recover its hold. Ogilvie (*Lancet*, August 4, 1894) recommends a more prolonged preliminary

<sup>1</sup> The authors are indebted to Mr. E. G. Fearnside of Trinity Hall, Cambridge, for this and for the other paragraphs on eosinophilia which will be found in the account of the more important parasites.

treatment, including dieting ; and, with the view of removing any mucus which might protect the parasite from the action of the drug, Carlsbad salts or other saline aperient for several mornings before active treatment is begun.

*Filix mas*, when fresh and well prepared, is perhaps the most reliable tæniafuge we possess. The *Extractum filicis liquidum* is best given in emulsion or in milk or in capsule, in three or four doses, of half a drachm each, at intervals of half an hour. As the cathartic, calomel (five grains) with scammony (eight grains) is efficient ; or a full dose of castor oil may be given with the last dose of the extract.

Pomegranate root is a good anthelmintic. It may be used either as the official decoction, or as a decoction prepared by macerating two ounces of the bruised bark in twenty-four ounces of water for twenty-four hours, and then boiling down to eighteen ounces and straining. Of the last-mentioned preparation a third part should be given at intervals of half an hour, the last dose being followed by a purgative.

A better preparation of pomegranate, and one which is coming much into use on the Continent, is the sulphate of pelletierine, prepared from the active principle of the bark. It is usually given in one dose of five to seven grains, with an equal quantity of tannic acid, in sweetened water. This is the dose for adults. For young people the dose must be considerably smaller ; it ought not to be given at all to children under eight or ten. The tannin—contrary to the general impression—does not add to the anthelmintic powers of the alkaloid ; it is given as a stomachic, and tends to diminish nausea and the risk of vomiting. After from a quarter to half an hour the cathartic should be administered. In from fifty to eighty per cent of cases the entire tapeworm is expelled. In toxic doses the action of pelletierine resembles that of curara, paralysing the motor nerve terminals, but not affecting muscular irritability. If the dose be too large it may give rise to vertigo, nausea, vomiting, diplopia and other visual troubles, pallor, cramps, and so forth. With the doses mentioned, and if the recumbent position be maintained for some hours, such effects need not be apprehended.

Kousso, in doses of four to eight ounces of the official infusion, is very effective when the drug can be obtained quite sound and fresh.

Oil of turpentine, in doses of from two to four drachms in emulsion, is sometimes prescribed ; but it is more nauseating and otherwise more objectionable than the drugs already mentioned.

For young children a safe tæniafuge is bruised pumpkin seeds : an ounce of the bruised seeds made into an electuary is not a disagreeable mixture and is readily swallowed.

After the action of an anthelmintic the head of the tapeworm should be diligently sought in the stools ; for, unless this is found, there can be no assurance that the cure will prove permanent.

## CLASS II.—TREMATODA

The trematodes are usually flat, leaf-shaped, unsegmented platyhelminthes, possessing a mouth and a pharynx. The latter bifurcates into two simple or branched intestinal tubes which terminate cæcally. They are provided with ventrally placed suckers, and are generally hermaphrodite. In a few species the sexes are separate.

Excretion is effected by a series of ramifying vessels which unite to form trunks terminating in a contractile vesicle, and finally opening at the posterior pole. The male organs of generation consist of testes (two), and vas deferens—the protrusible end of which forms the cirrus or penis. The female organs of generation comprise an ovary, yolk-glands (two), shell-gland, convoluted uterus, and vagina. The sexual openings are placed close together on the ventral surface.

The order is divided into several families.

So far as known, the trematodes occurring in man are oviparous. The ovum at birth in some species contains a ciliated embryo; in other species this embryo is not developed until later. In either case, after leaving the uterus of the parent the ovum is carried in the discharges of the host into water or into damp soil. Here, after a variable time, the ciliated embryo—the *miracidium*—is hatched out, and for a short period swims about in search of its special intermediate host. Should it succeed in finding this—usually a mollusc or crustacean—the embryo, selecting some weak point unprotected by shell or dense integument, drills its way, by means of the little beak with which it is provided, into the body of this animal, and therein, losing its ciliated covering, enlarges and becomes transformed into a *sporocyst* (a sort of hollow sac having no alimentary canal), or into a *redia* or larva provided with an alimentary canal. In the interior of the sporocyst or of the redia, and originating from certain germ cells, tailed *cercariæ* are developed; or, it may be another generation of sporocysts or rediæ is produced. The minute *cercariæ*, originating in the sporocysts and rediæ, resemble distomes in the possession of suckers and alimentary canal, but differ from the mature worm, inasmuch as they are destitute of organs of generation; and, further, in that they are usually provided with actively moving and powerful tails. When sufficiently mature the *cercariæ* spontaneously quit the sporocyst or redia. Leaving now the body of the intermediary host, they swim about in the water, or creep about in damp places, and may become encysted on blades of grass, leaves, or in the mud, or they may come across a second intermediate host—mollusc, worm, insect, larva, or fish—into the tissues of which they enter, and in which, having dropped their tails, they become encysted. However this may be, either in the body of intermediate host, or encysted on some vegetable, or in water, the cercaria finally enters the body of the definitive host. It then finds its way to its proper habitat the intestine, bile-ducts, lungs, blood-vessels, or other tissue, and rapidly develops into the sexually mature distome.



The nature and classification of the minute parasite (0·21 mm.) found by von Nordmann in the cataract of an old woman, and named *Monostoma lentis* von Nordm. 1832, is doubtful.<sup>1</sup> The *Distomum oculi humani* Amnon 1833 (Synonym: *D. ophthalmobium* Diesing 1850) also requires reinvestigation. Amnon found four examples, 0·5 to 1 mm. in length, between the lens and the capsule of the eye of a five-year-old child. Leuckart regarded these as specimens of *Dicrocoelium lanceatum*; others have suggested they are young leeches (Fig. 140).

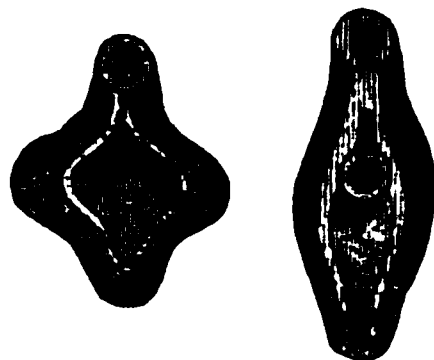


FIG. 140.—*Distomum oculi humani*. Leuckart.

The large and unwieldy family Distomidæ has been and is being broken up into a number of new families of which three include trematodes parasitic in man.

### Family I. Fasciolidæ

The Fasciolidæ possess an oral and ventral sucker; the excretory system opens on the posterior edge; the reproductive pore is median, in front of the ventral sucker; the primary diverticula of the alimentary canal are mostly without secondary branches; hermaphrodite.

i. *Fasciola hepatica* (Linn.) 1758.—(Synonyms: *Distomum hepaticum* Retz. 1786, *F. humana* Gmel. 1789, *Distomum carice* Sons. 1890, *Cladocœlium hepaticum* Stoss. 1892) (Fig. 141).—The normal habitat of the liver-fluke is the bile-ducts of the sheep. Occasionally it is found in a similar situation in man, more often in certain ruminants and rodents. Besides having been found in man in this its normal habitat, it has three times been found in various veins (the *Hexathyridium venarum* of Treutler was probably a misplaced *F. hepatica*), and four times it is recorded as having been removed from subcutaneous tumours in which it had developed, having been carried there probably, whilst immature, in the blood. It is sometimes found in the lungs of the ox.



FIG. 141.—*Fasciola hepatica* (nat. size). After Leuckart.

The mature parasite is a long, flat, brownish, leathery, leaf-shaped animal possessing considerable activity, and measuring from 20 to 30 mm. in length by 8 to 13 mm. in breadth. The oral sucker, which is the smaller, is placed at the top of a sort of protuberance—representing, so to speak, the stalk of the leaf; it contains the buccal orifice. A very short distance behind this is the ventral sucker, in front of which again lies the opening of the genital organs (Fig. 143). The cuticle is covered with fine spines directed backwards.

Lying in the bile-ducts the liver-fluke pours its large, brown, oper-

<sup>1</sup> Braun suggests that it is not impossible that this form was a young, minute leech.

culated eggs (0.13 by 0.08 mm.)—very like, but about twice the size of those of *Dibothriocephalus latus*—into the bile. Passing out with the dung, in favourable circumstances they are carried into water where, after a variable period of from two to three weeks to as many months according to temperature, the ciliated miracidium is developed. When sufficiently mature the embryo forces open the operculum, and escapes into the water. It then enters a small mollusc—*Limnæa truncatula*, or other and closely allied species of gastropod—in the pulmonary cavity of which it

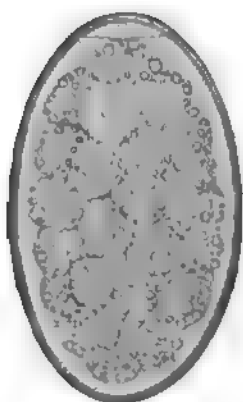


FIG. 142. — Egg of *Fasciola hepatica* (x about 400). Light yellow brown in colour. From Loos<sup>2</sup>.



FIG. 143. — *Fasciola hepatica*, showing ovaries, uterus, and testicular structures (x 24). Leuckart.

passes through the sporocyst, redia, and cercaria stages of development. Finally, escaping from the intermediate host, it may encyst itself on some aquatic plant; and while in this stage, or while still in the intermediate host, or swimming, or creeping about as a free cercaria, it is transferred to the stomach of sheep or ox, and so to the biliary passages. Doubtless man becomes infected from drinking-water fouled by "flukey" sheep or cattle, or from eating aquatic plants on which cercariæ had encysted themselves. The duration of the stay of the fluke in the bile-ducts is not accurately known. Some suggest nine months, others a year or longer. That they do leave the ducts spontaneously is certain, for they are sometimes passed per anum and even vomited.

In the sheep *F. hepatica* gives rise to the important epizootic known as "sheep rot," a disease characterised by anæmia, emaciation, ascites and cedema, and enlargement of the liver. It is very fatal, and is specially common in flocks pasturing in certain low-lying localities in which *Limnæa truncatula* and other minute gastropods abound. In some of the cases in which it occurred in man, it appears to have given rise to no particular symptoms; in other instances it has caused dilatation, thickening, and obliteration of the biliary passages, enlargement of the liver, and thickening of Glisson's capsule, or even abscess of the liver. These pathological conditions were associated with a variety of symptoms, such as vomiting, diarrhoea, constipation, hepatic pains, ascites, jaundice, enlargement of the liver, fever, and so forth. In obscure hepatic affections, therefore, the vomiting or the passage of flukes per anum, or the discovery of their characteristic ova in the stools, would indicate a probable explanation of the symptoms.

ii. *Fasciolopsis buski* (Lank.) 1857.

—(Synonyms: *Distomum buski* Lank. 1857, *D. crassum* Busk 1859, nec v. Sieb. 1836) (Fig. 144).—This, the largest of the distomes occurring in man, has been found in the alimentary canal of a considerable number of Europeans living in the East, in East Indians, particularly in Chinese in Canton, Borneo, and the Straits of Malacca, and in natives of Assam and India. Recent investigations seem to shew that both it and certain other

and as yet unidentified distomes are by no means the rare parasites they were formerly supposed to be. Dobson, in the stools of 1249 unselected Indian coolies to whom he had administered a large dose of thymol, found large (*Fasciolopsis buski*) and small (*Gastrodiscus hominis*, *Opisthorchis noverca*, and *O. sinensis* (?)) distomes thirteen times, or in rather over 1 per cent. of the cases. In the three instances recorded by Cobbold—father, mother, and child—the parasite, which evidently had been acquired near Ningpo, China, appeared to give rise to a certain amount of intestinal irritation and to dyspeptic symptoms accompanied by

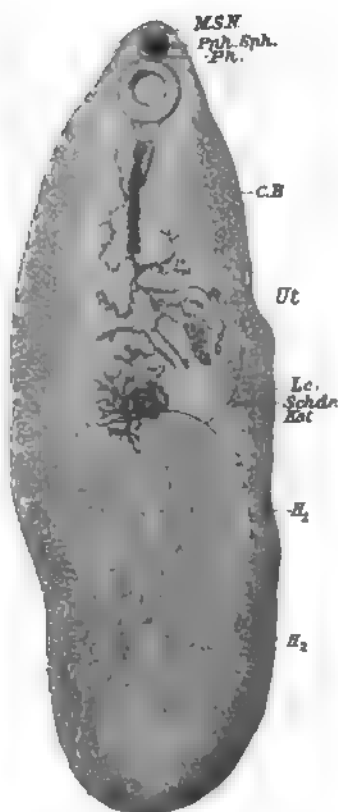


FIG. 144.—*Fasciolopsis buski* (magnified). From Oshner. C.B., cirrus recessa; H<sub>1</sub> and H<sub>2</sub>, testes; Ov., ovary; Lc., Laurer's canal; M.S.N., oral sucker; Ph., pharynx; Lph. Sph., peripharyngeal sphincter; Sch. dr., shell-gland; U<sub>1</sub>, uterus.

irregular diarrhoea of pale stools, occasionally streaked with blood. In the other recorded instances there is no mention of any particular clinical symptom attributable to the parasite.

*Fasciolopsis buski* is easily recognised by its great size—24 to 37 and even 70 mm. in length by 5·5 to 12 or even 14 mm. in breadth. It is thick, brown, smooth and without spines, and oblong in shape, the posterior part being somewhat the wider. The ventral sucker, which is the larger (1·6 mm.), can be readily seen by the naked eye close behind the oral sucker. The eggs are oval (0·125 mm. by 0·077 mm.), have granular contents, and are operculated. The line marking the operculum is very delicate, and is, therefore, apt to be overlooked (Figs. 145, 146).

iii. *Fasciolopsis rathouisi* Poirier 1887. — Length 25 mm. by 16 mm., no spines, the suckers approach one another. The testes and

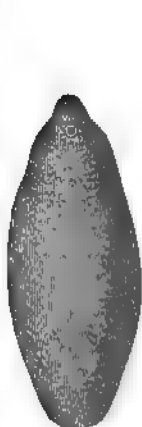


FIG. 145. *Fasciolopsis buski* (nat. size). Leuckart.

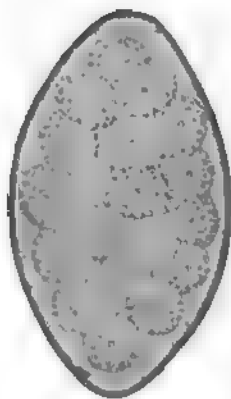


FIG. 146. Egg of *Fasciolopsis buski* (x about 400). Light brown in colour. From Looss.

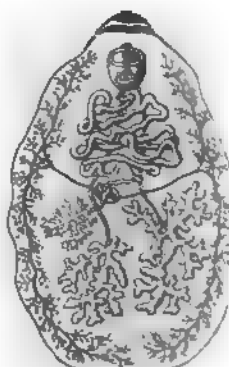


FIG. 147. — *Fasciolopsis rathouisi*. From Braun.

ovary lie posteriorly. The eggs measure 0·15 by 0·08 mm. This has been observed in a Chinese suffering from liver disorder and possibly again in a Chinese and a Malay in North Borneo.

The life-history of this Trematode is quite unknown.

iv. *Dicrocoelium lanceatum* Stil. and Hass. 1896. — (Synonyms: *Fasciola lanceolata* Rud. 1803 (*nec* Schrank 1790), *Distomum lanceolatum* Mehlis 1825, *Dicrocoelium lanceolatum* Dujardin 1845.) — This distome, which in ruminants is frequently associated with *F. hepatica*, is recorded as having been found in man seven times. It is somewhat lancet-shaped and broader posteriorly than anteriorly. It measures from 8 to 10 mm. by 1·5 to 2·5 mm., is thin, supple, and devoid of cuticular spines. The dark ova (0·04 by 0·03 mm.) are provided with a double-outlined, operculated shell, and contain, even at birth, a fully developed miracidium, the cilia of which, however, cover the anterior third of the body only. The intermediate host is believed to be the

mollusc *Planorbis marginatus*. It has also been found in the alimentary canal of the slugs *Arion* and *Limax*. The adult lives in ruminants, rabbits, and swine.

From its small size this distome is not likely to damage the bile-passages seriously, and in none of the cases in which it has been found—

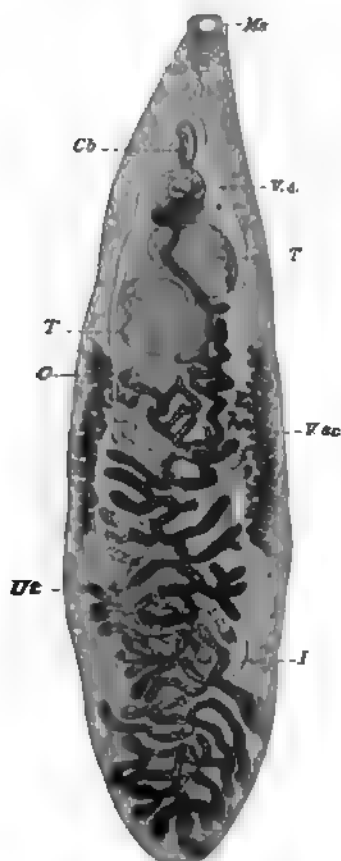


FIG. 148.—*Distocotylum lanceatum* ( $\times 15$ ). From Braun. Cb, cirrus sac; I, intestine; Ms, mouth; O, ovary; T, testis; U, uterus; V.s, ventral sucker; V.sc, yolk-glands.



FIG. 149.—Egg of *Distocotylum lanceatum* ( $\times$  about 400). Deep brown in colour From Looss.

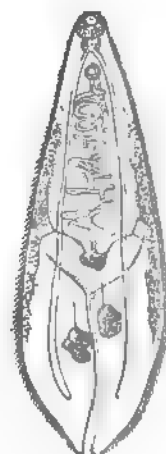


FIG. 150.—*Opisthorchis noverca* ( $\times 6$ ). After McConnell.

with perhaps one exception—could it be regarded as the cause of grave hepatic trouble.

v. *Opisthorchis noverca*. Braun 1903.—(Synonym: *Istoma conjunctum* Lew. and Cunn. 1872) (Fig. 150).—This parasite has twice been found in man by McConnell in Calcutta. Both patients were East Indians who had died from dysentery. The distomes were present in

large numbers—upwards of 100 in both cases, and lay in the dilated bile-ducts, from which they escaped on section of the liver.

*Opisthorchis neverca*, in size and outline something like a flattened oat-seed, measures on an average 9.5 to 12.7 mm. by 2.5 mm. It is distinguishable from *D. lanceatum* and *O. sinensis* by the minute spines with which it is covered, as well as by the arrangement of its viscera. The ova have a double outline, are operculated, and measure 0.034 by 0.021 mm. Nothing is known of its life-history, apparently it is not uncommon in the liver of pariah dogs in India.<sup>1</sup>

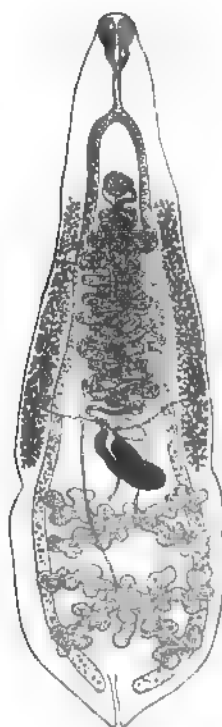


FIG. 151.—*Opisthorchis sinensis* (x 5). Leuckart.

vi. *Opisthorchis sinensis* (Cobb.) 1875.—(Synonyms: *Distoma sinense* Cobb. 1875, *I. spathulatum* R. Leuck. 1876 (*pec* Rudolphi 1819), *D. hepatis endemicum* s. *perniciosum* Baelz 1883, *D. hepatis innocuum*, Baelz 1883, *D. japonicum* R. Blanch. 1886) (Fig. 151).—Recent investigations seem to indicate that this distome has an extended geographical distribution, that in some places it is widely endemic, and that in such places it is of considerable pathological importance. Discovered by McConnell in a Chinaman in Calcutta in 1874, it has since been frequently found in the same race in Mauritius and in the Straits of Malacca. It has also been found in natives in Assam and in Corea. In Japan, according to Baelz, it is common in places. He describes, under the names *D. hepaticum perniciosum* and *D. hepaticum innocuum*, what seems to be this parasite, or varieties of it, as occurring in great abundance in 20 per cent of the population of certain damp, insalubrious seaside villages of the province of Okayama which have an unwholesome water-supply.

In these villages, and probably elsewhere in places in which it is endemic to a severe degree, it gives rise to a train of symptoms characterised at first by morbid hunger, epigastric weight and pain, enlargement and tenderness of the liver, and swelling of the spleen. After a few years diarrhoea, ascites, œdema of the legs, and a cachectic condition supervene and, in the long run, lead to death. At post-mortem the liver is found enlarged, and a number of diverticula, about the size of a filbert or small nut, containing hundreds of distomes, are discovered in association and communicating with the gall-bladder and bile-ducts. Distomes are also found free in the bile-ducts and sometimes in the duodenum. Around the diseased bile-ducts the hepatic tissue is atrophied.

*O. sinensis* measures on an average 18 mm. in length by 4 mm. in

<sup>1</sup> Cobbold has described an allied but specifically distinct form in bile-ducts of *Canis fulvus*.



breadth. Though somewhat larger, in general appearance it resembles very closely *O. norecca*. Unlike this form it has no epidermic spines. In the preserved state the measurements are 10 to 14 mm. by 2.4 to 3.9 mm. In *O. sinensis* the oral sucker (1.0) is larger than the ventral (0.8). Other points of difference will be readily appreciated by comparing the figures of these liver Trematodes. The ova of *O. sinensis* are oval, granular with a double outline, and are operculated; they measure 0.027 mm. by 0.016 mm.



FIG. 152. Egg of *Opisthorchis sinensis* (x about 400). Light brown in colour. From Looss.

Further than that it is occasionally found in the domestic dog and in the cat nothing is known of the life-history of this parasite.

vii. *Opisthorchis felineus* Riv. 1885.—(Synonyms: *Distoma conus* Gurlt 1831 (nec Creplin 1825), *D. lanceolatum* v. Sieb. 1836 v. Tright 1889 (nec Mehlis 1825), *D. sibiricum* Winogr. 1892, *D. tenuicollis* Mühl. 1896.)—This trematode has a yellowish-red, transparent, flattened body, with a rather conical anterior end. Length 8 to 11 mm., breadth 1.5 to 2 mm. Eggs with opercula, 0.03 by 0.011 mm. This is a common parasite in the gall-bladder and bile-duct of cats and more rarely of dogs, but it occurs in man throughout northern Europe, and is perhaps the commonest human parasite in Siberia.



FIG. 153. — Egg of *Opisthorchis felineus* (x about 400). Light yellow brown in colour. From Looss.

Its life-history is unknown.

viii. *Cotylogonimus heterophyes* (v. Sieb.) 1852.—(Synonyms: *Distomum heterophyes* v. Sieb. 1852, *Mesogonimus heterophyes* Raill. 1890, *Cænogonimus heterophyes* Looss 1900) (Fig. 154).

—This exceedingly minute Trematode was first found by Bilharz in 1851 about the middle of the small intestine of Egyptians in Cairo; Looss and Blanchard have also described cases. It occurs in masses, and the distomes look to the naked eye like minute red points. The parasitic nature of these red points is apparent on their being placed under the microscope. The individual distomes measure about 1.15 to 2 mm. in length by 0.7 to 1 mm. in breadth. They are readily diagnosed by the smallness of their size and by the character and position of the ventral sucker, which, proportionately speaking, is unusually large (0.35 mm.), and is located slightly in advance of the middle of the body and in front of the sexual opening. The ova (0.03 by 0.017 mm.) have a thick, reddish-brown shell, the colour of which is communicated to the entire animal.



FIG. 154. — *Cotylogonimus heterophyes*. Leuckart.

Nothing, except that it is common in dogs, is known of the life-history of this parasite, nor of any associated pathological condition.

ix. *Paragonimus westermani* (Kerb.) 1878.—(Synonyms: *Didymus westermani* Kerb. 1878, *D. ringeri* Cobb. 1880, *D. pulmonale* Bach 1883, *D. pulmonis* Suga 1883, *Metagonimus westermani* Raill. 1890) (Figs. 157 and 158).—This distome is

parasitic in the lungs of man in Japan, China, Corea, and Formosa, where, in particular districts, a large proportion of the inhabitants are affected with the peculiar form of hæmoptysis to which it gives rise. Hitherto it has not been described as occurring in man in any other region; although, seeing that it has been found in the tiger, the cat, the dog, and in swine, it is more than

probable that its geographical range is not limited to the countries mentioned. Recently it has been found in both the cat and the dog in the United States. There are some



FIG. 155. Egg of *Colpogonimus heterophyes* ( $\times$  about 400). Dark reddish-brown in colour. From Loosa.

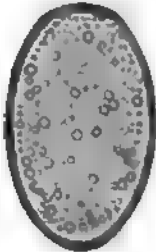


FIG. 156.—Egg of *Paragonimus westermani* ( $\times$  about 400). Light yellow to reddish-brown in colour. From Loosa.



FIG. 157.—*Paragonimus westermani* (nat. size). Leuckart.



FIG. 158.—*Paragonimus westermani* magnified. Leuckart.

grounds for the opinion that it is a parasite of countries with a volcanic soil.

*P. westermanni* is from 8 to 10 mm. in length, by 4 to 6 mm. in breadth. It is oblong in shape; very thick for a distome, being nearly circular on transverse section; leathery in consistency, and brownish-red in colour. The ventral sucker, close behind which is the genital opening, is placed about the middle of the junction of the anterior with the middle third of the body. The eggs (0·08 to 0·1 mm. by 0·052 to 0·075 mm.) are oval, operculated, brownish-red, double outlined, and filled with granular contents, the embryo being not yet differentiated.

The mature distomes live in tunnels or burrows, with thick connective-tissue walls, situated principally under the pleura and near the surface of the lung. These burrows, from the breaking down of the septa between the tunnels, are sometimes converted into cyst-like cavities, which may be the size of a filbert. These cavities communicate with the bronchi by finer or larger sieve-like openings through which an ova-laden, rusty-coloured, viscid muco-pus escapes into the air-passages. This secretion excites cough and is expectorated. Several distomes may inhabit the same burrow; as many as twenty have been found in one lung. *P. westermanni* has also been found in the cortex of the brain in two cases of a peculiar and fatal form of Jacksonian epilepsy; it has also been found beneath the peritoneum, in the orbit, and in the scrotum. It is evident that this parasite is very apt to lodge in different parts of the body and away from its normal habitat, the lungs.

The symptoms of paragonimiasis, or endemic hæmoptysis as it is sometimes designated, are a chronic cough—usually worst in the morning, a persistent pneumonic-like sputum in which ova abound, and recurring attacks of more or less profuse hæmoptysis, the exact and immediate mechanism of which has not yet been explained. Little can be discovered by auscultation in the earlier stages; but in chronic cases of extreme degrees of infection signs of consolidation and perhaps of cavity may be made out. The disease lasts for many years and may prove fatal. It appears to be incurable, although cases have been met with in which the patient had, after many years, ceased to cough and expectorate the characteristic sputum.

In the natives of countries in which *P. westermanni* is endemic the concurrence of pulmonary paragonimiasis with cerebral symptoms ought to suggest the probability that the latter are dependent on the presence of trematodes in the brain. In such a case, if the symptoms be of a focal character and attributable to a cortical lesion, the propriety of removal of the parasite by surgical means might be entertained.

When the ova contained in the sputum are well washed and kept in a moderately warm room in fresh water, after a variable time of two to six weeks, according to temperature, a ciliated miracidium is developed in their interior. On arriving at maturity the miracidium escapes into the water by throwing back the operculum at the broad end of the shell. It is probable, therefore, that the intermediate host of *Paragonimus* is a fresh-water animal. Katsurada, who is to some extent supported by Yamagiwa, believes that the young enter the stomach of

man and bore through the intervening tissues until they reach the lungs; this is little more than conjecture. Except that the ova hatch out in water nothing is really known of the life-history of this important and very dangerous parasite; this point, however, is of practical value as indicating the direction prophylactic measures should take.

## Family II. Paramphistomidæ

The anterior end of the body is pointed; the posterior is broad and hollowed out, and on the hinder end of this hollow is the ventral sucker: dorsal to this the excretory pore opens; intestinal cæca with no branches, the pharynx pushed forward and usually described as an oral sucker: hermaphrodite.

i. *Gastrodiscus hominis* (Lew. and McConn.) 1876. — (Synonym: *Amphistomum hominis* Lew. and McConn.) (Fig. 159).—First described by Lewis and McConnell from specimens found in an Assamese, until lately this parasite appeared to be very rare. If, however, the expression “small distomes,” used by Dobson in his description of the trematodes met with during the investigations already referred to (p. 855), applied to this parasite, it cannot be uncommon in India and similar climates. It is thought to be normally a parasite of the horse, and that occasionally it finds its way into man. In the two cases from which Lewis and McConnell obtained their specimens

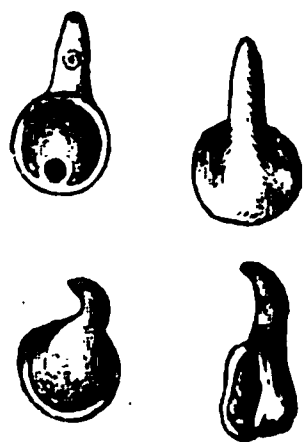


FIG. 159.—*Gastrodiscus hominis*. Leuckart.

the parasite occurred in hundreds, and was found adhering with its posterior sucker to the mucous membrane of the cæcum, appendix, and ascending colon.

*G. hominis* is very minute, measuring only 5 to 8 mm. in length by 3 or 4 mm. in breadth at its broadest part—that is, across the posterior sucker. From the great relative breadth of the last-mentioned feature the little animal looks as if it consisted of two parts—of a disc and a short attached handle. At the end of this short handle the oral sucker is situated; between this and the posterior sucker, and on the ventral surface, the genital pore may be made out. The ova, which measure 0.15 mm. by 0.07 mm., have a firm, operculated shell.

Nothing is known of the life-history of the parasite, nor of the pathological conditions it may give rise to.

ii. *Cladorchis watsoni* (Conyngham) 1904. — (Synonym: *Amphistomum watsoni* Conyngham 1904) (Figs. 160 and 161).—This parasite was first found in numbers in the duodenum and upper part of the jejunum of a freed slave who came from Adamawa in German West Africa, and died in Northern Nigeria. Recent information would seem to indicate that this parasite is extremely common in certain parts of Northern Nigeria, especially in the neighbourhood of Lake Chad.

Children especially are liable to infection and sometimes die, probably from the associated anæmia. As regards treatment, we have no positive

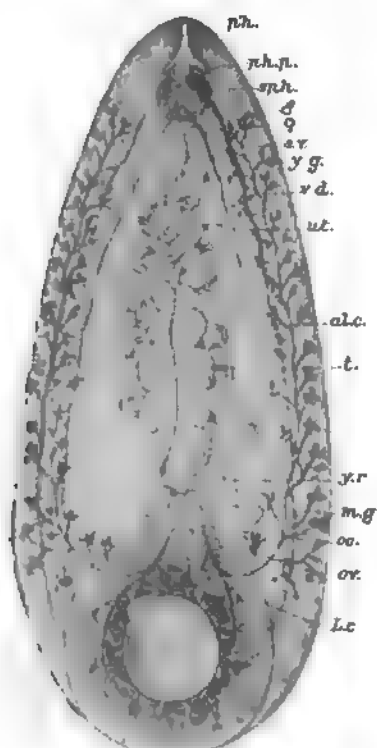


FIG. 160.—Diagram of *Cladorchis watsoni*. a.l.c., alimentary canal; L.c., Laurer's canal; m.g., shell-gland; oo., ootype; ov., ovary; ph., pharynx; ph.p., pharyngeal pouches; sph., sphincter muscle around oropharyngeal bulb; s.v., seminal vesicle; t., testes; ut., uterus; v.d., vas deferens; y.g., yolk-glands. (Shipley.)



FIG. 161.—*Cladorchis watsoni*. a, ventral surface, natural size; b, anterior aspect magnified; c, ventral surface magnified. g.p., genital pore. (Shipley.)

knowledge of any specific, but it is probable that thymol or eucalyptus oil combined with purgatives will, as in ankylostomiasis, be effective. Its normal host is probably some herbivorous mammal.

P. M.  
A. E. S.

### Family III. Schistosomidae Looss

In structure resembling the Fasciolidae, but bisexual.

*Schistosomum hæmatobium* (Bilharz) 1852.—(Synonyms: *Distoma hæmatobium* Bilharz, *Distoma capense* Harley 1864.)

## BILHARZIASIS

By F. M. SANDWITH, M.D., F.R.C.P.

SYNONYMS.—Bilharzia disease, endemic hæmaturia, Egyptian hæmaturia

**Definition.**—A chronic, endemic human disease of many African countries, characterised by hæmaturia, cystitis, rectal irritation, and other symptoms; in young females the vagina and uterus may be invaded. In advanced cases there are many serious complications, which may eventually cause the death of the patient. The symptoms are caused by the deposit in the tissues of numberless eggs laid by the *Schistosomum hæmatobium* worm.

**History.**—It is probable that the parasite has been domiciled in Egypt for hundreds of years, because the natives have long suffered from hæmaturia and from urinary calculi partly due to this cause. We know that in 1799-1801, during their occupation of Egypt, the French troops suffered much from hæmaturia without discovering the cause. In 1851, Bilharz, in Cairo, first found that Egyptian hæmaturia was due to the worm which is often named after him; and in 1864, Dr. John Harley, in London, recognised the disease in persons coming from South Africa.

Bilharz and Griesinger found the parasite in Cairo in 32 per cent of 363 autopsies; a few years later, between 1875 and 1883, Sonsino found bilharzial infection in 46 per cent of 91 post-mortem examinations in Lower Egypt; and Kaufmann, in 1893, recognised the parasite in 33 per cent of 500 autopsies in Cairo.

**Geographical Distribution.**—The disease is nowhere endemic in Europe; but imported cases are frequently heard of, and there are at least two instances of the affection occurring in England in individuals who had never been out of this country. Berkeley Hill reported a case of a woman, aged 40, admitted into University College Hospital in 1887 suffering from hæmaturia due to bilharziasis, who had never lived out of the county of Kent. Major Freeman records another case of a private soldier, aged 24, who was admitted for bilharziasis to the Military Hospital at Colchester in January 1905; it was impossible to discover by what means he had become infected, but it was suggested that urine from some unknown patient who had returned from South Africa with bilharziasis had infected the barrack-room in which this soldier, who had never been out of England, spent some days.

In Asia the affection has been reported from the Hedjaz (Mecca), Arabia, Syria, Mesopotamia, in the valleys of the Tigris and Euphrates, Persia, Mauritius, and the West Coast of India. Sporadic or imported cases have been known in Cyprus, Penang, and Shanghai. The special *Schistosomum* lately discovered in Asia is dealt with on page 881.

The bilharzia disease is best known and most widely distributed in Africa. In Lower Egypt the worm is still found in at least one-third



of all the autopsies; in Upper Egypt it is distinctly less common. In the Sudan it is frequently met with among imported Egyptians, and Dr. Balfour has recently found it in three boys who had never been out of the Sudan. Sporadic cases have been reported in Arabs from Kassala, Darfur, and Kordofan, while the disease is endemic in Tunis and Algiers. On the West it is known on the Gold Coast, in Nigeria, the German Cameroons, and Angola; and on the East Coast all the way from Suez to the Cape of Good Hope, especially in Abyssinia, where the Italian troops suffered seriously from it during their campaign, Zanzibar, and the Mozambique coast, and in Madagascar. In Central Africa it is endemic in Uganda, British Central Africa, and the Congo State. Looss found in 1905 that one (the youngest boy, aged 12) of the six pygmies brought from the Ituri forest in the Congo Free State had bilharzia eggs in his faeces, but not in his urine. In South Africa the disease is well known in Delagoa Bay, Natal, Port Elizabeth, Bloemfontein, the Transvaal, and Kaffraria, but the complications are fewer and less serious than in Egypt.

Single cases have at rare intervals been reported from Illinois and other parts of the United States, and Gunn has described the cases of two patients who came from Porto Rico and had resided for a few months in the Hawaiian Islands: in both these patients eggs were found in the faeces only. Sir P. Manson has reported one case from the West Indies in an English resident who had lived in several of the islands; in this patient, and in Letulle's case from Martinique, the rectum only was affected.

**Natural History of the Parasite.**—The best account of the life-history of the worm is in the article in Mense's *Handbuch der Tropenkrankheiten*, by Professor Looss. I have borrowed freely from his article, and have obtained permission to use three of his drawings.

The *Schistosomum hæmatobium* is one of the two-sexed trematode worms; the male is about 1 cm. in length, and to the naked eye looks white in colour and cylindrical, but tapering at each end. Under the microscope the oral and ventral suckers are to be seen one behind the other. The body of the male is closely covered with small tubercles, and behind the ventral sucker there is an opening which seems to lead into the body, but is the beginning of the gynæcophoric canal. This is formed by the folding inwards and overlapping of the lateral parts of the body, which is really flattened in the shape of a leaf. The female (2 cm.) is much longer than the male, so that part of her body often protrudes from the canal, and yet she sometimes hides herself so completely within it that she can only be discovered by the aid of the microscope. As partly seen in Fig. 162, only the upper part of her thread-like body is white, the lower half being grey and traversed by a dark brown zig-zag stripe which represents the intestinal canal filled with blood. The sexes live apart while young, but directly they become mature the female enters the gynæcophoric canal of the male, since she is chiefly dependent on him for powers of locomotion. The worms found in the liver are always young,

and when couples in conjunction are seen in the portal vein, which is their principal habitat, the female has very few eggs in her uterus and those eggs are not normal. Bilharz originally found coupled worms in the intestinal veins and in the wall of the bladder, and noticed that the females in the bladder contained plenty of mature eggs. It appears, therefore, that complete maturity is not reached until the worms approach the veins of the pelvis. The males, starting from the portal vein and

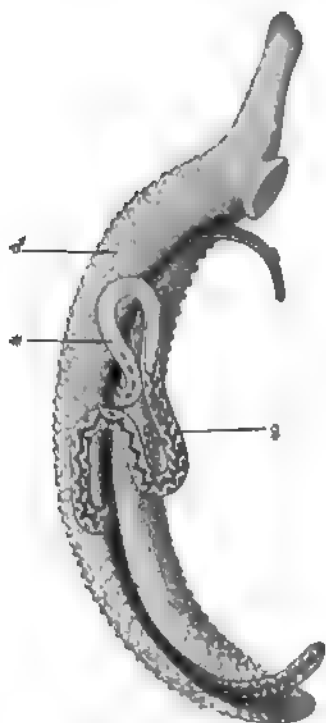


FIG. 162.—A coupled pair drawn from life.  $1 \times 12$ . The star marks the ootype, in front of which are eggs. Looss.

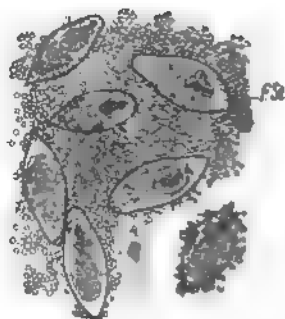


FIG. 163.—Eggs of different shapes in urinary deposit, the two most normal being below on the left. F.S. marks an egg with a slightly deviated spine. Looss.

carrying the females with them, make for the submucous tissue of the bladder and rectum, by means of energetic movements of their strong muscles, Looss has sometimes seen these organs so rich in worms that a pair may be found in every area of half a cm. square. The eggs are deposited by the female in the veins: they are elliptical, and somewhat pointed at each end, and measure on an average 0.08 by 0.03 mm. Segmentation occurs after their entry into the tissues, and the eggs grow until they are about 0.11 to 0.12 mm. long and 0.04 to 0.05 mm. wide. Their thin yellow shell has at its posterior end a small pointed spine; but often another form of egg is seen with a considerably larger

spine at the side, and occasionally eggs are met with which have no spine at all. Eggs with a terminal spine are usually found in the urine, while in the feces lateral-spined eggs are often present, but this is not a universal rule. Sir P. Manson has suggested that two species of the parasite probably exist, one producing eggs with terminal spines, and the other eggs with lateral spines, the latter being a worm frequenting the hæmorrhoidal vessels. In support of this conjecture he adduces the fact that the only cases of bilharziasis hitherto reported from the West Indies have been patients with rectal symptoms with lateral-spined ova in their feces. If the disease should eventually be shewn to be common in the West Indies it will certainly be interesting to try to discover why the urinary form of the disease, associated with terminal-spined eggs, is not also present. It is, however, more probable, as Looss has suggested, that the eggs with the lateral spines are abnormally formed specimens. Like Bilharz, he has found them chiefly in isolated females, and he suggests that it is only the immature females who lay eggs with lateral spines, and that these are malformed, from mechanical reasons, in the uterus.

The eggs are expelled from the uterus before the worms reach the capillaries, at some time during their journey from the portal vein to the pelvic veins, and are mostly carried along by the blood; though a few, especially those with lateral spines, may remain in some organ such as the liver. When once the worms have reached the capillaries of the pelvic organs, most of the eggs are held fast by the pressure of surrounding tissues to the spot where they were first deposited, and therefore bilharziasis is originally a local manifestation. The eggs are squeezed together by the contracting muscles of the bladder or rectum, and penetrate into the tissues until they reach the surface, and are expelled with the excreta. Those with a lateral spine cannot proceed in a straight line because of their misplaced steering apparatus, and they therefore tend to collect in the tissues, especially in the bladder. If all the eggs escaped with the excreta, there would be few symptoms and almost no complications. Many eggs die during their process of development, and therefore they vary in size according to the stage of growth at which they have arrived before their death; but when living eggs are passed in the urine or feces of a patient they generally contain a ripe ciliated embryo, which is known as the *miracidium*. The miracidium will not hatch from the egg in urine, but if fresh water be added to the slide it emerges from the egg in a few minutes, in warm weather, and swims about very rapidly by means of its cilia. But although water of a certain warmth is obviously essential for the life of the miracidium, no one has yet succeeded in

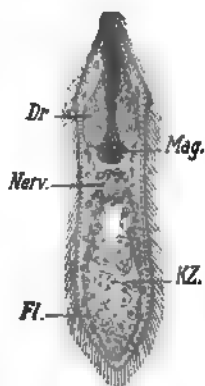


FIG. 104 A free-swimming miracidium. *Dr.* is one of the two large head-glands, *Mag.* the stomach cavity, *Nerv.* the nervous system, *KZ.* the germinal cells. Looss.

keeping it alive for longer than 30 or 40 hours, and all experiments made with the object of transferring it to molluscs and other animals which might possibly act as intermediary hosts, have so far failed.

**Infection of Man.**—By the analogy of other trematode worms, it has for years been supposed by most writers that the miracidium must enter some animal as yet undiscovered, arrive at the human stomach with unfiltered drinking-water, and then develop into bilharzia worms. Now bilharziasis is such a widely spread disease in Lower Egypt that it is fairly obvious that if any intermediary host exists it cannot be any creature of great rarity, and systematic search among the molluscs of the Delta has so far yielded no trace of any developmental stages of the *Schistosomum*. Looss has long argued that the miracidium enters directly into man; and he excludes the possibility of entry by the mouth in drinking-water, because the embryo cannot live for one minute in a solution of 1:1000 hydrochloric acid, nor for three minutes in a solution of 1:2000. The acidity of the human stomach is said to be 4:2000 (.2 per cent), so that it does not seem possible for the miracidium to emerge alive from the human stomach, if it ever gets there. The infection of man's stomach directly by the miracidium is a notion which should be abandoned. It has been seriously suggested by several writers that entry can occur by the urethra or rectum, but there is no evidence in support of this.

There remains for discussion the mode of entrance by the skin, in which Looss is a firm believer. It was long ago suggested as the possible explanation of the fact that bathers are especially attacked by this disease; and as men and boys bathe in South Africa (as in most other countries) more commonly than girls, it was thought by Drs. J. Harley, Brock, Felkin, and others that this difference in their habits might account for the comparative immunity of the female sex. It is quite possible that those who believed that bathing caused the disease were right.

It has long been known that it is chiefly male earth-workers in country districts who suffer from the disease, while in towns it is especially the children who seem to be infected. This quite confirms the view that the parasite may enter by the skin, for in Egypt we find that in the poorest classes of peasants, where men and women work together in the fields, both sexes are apt to suffer equally from bilharziasis. When we examine those who are less poor, so that only the men are obliged to work on the land, the latter still suffer from the disease in much the same ratio as their poorer brethren, but the disease becomes rare among their women. Ascending still farther in the social scale, we find that in small landowners, clerks, and others not personally engaged in agricultural labour bilharziasis becomes rare even among the men (Talaat). Yet for all these three classes in country districts and for both sexes the drinking-water is the same, unfiltered, direct from the Nile or from Nile-water in a canal. This looks as if drinking-water had

nothing to do with the problem, and as if the causation were dependent upon the amount of skin surface of the individual exposed to the water. Critics object that the embryo is incapable by its formation of entering the human skin; but it is known that the miracidia of other trematodes succeed in penetrating the skin of various molluscs and then reach the liver. At present the hypothesis of skin penetration is not proved, because one hesitates to submit a volunteer to the risk of contracting a disease the cure of which is not known, but it seems evident that the bilharzia miracidium, when it does succeed in entering the human body, must get to the liver; for this is the only organ where very young worms are found, and it seems clear that they disperse from the nursery in the liver to other parts of the body. When they have reached maturity, the worms enter the large branches of the portal vein, join sexually, and travel on to the veins of the pelvic organs, where they lay their eggs. Some coupled pairs probably go astray on the way and lay their eggs, thus accounting for isolated bilharzia tumours in unusual places (Looss).

It is only natural that the hypothesis of infection through the skin should have found more believers among workers in Egypt since we have watched the successful development of Looss's experiments, which have satisfactorily proved that the larvæ of *Ankylostomum duodenale* can enter the skin of man, and that other allied species do penetrate the skin of man and animals. For the hypothesis of infection by the skin of the bilharzia miracidium it is only necessary that liquid mud or water, fouled by living eggs, should remain for a little while in contact with the human skin. In Egypt the middle-class and poor children of both town and country districts become affected because they play in small, dirty ponds where infection becomes easy if one of them urinates bilharzia eggs into the water, an event which constantly happens. But among adults it is chiefly the country-dwellers who suffer, partly because the town children, as they grow older, wear boots and cease to paddle in the ponds, and therefore run less risk of re-infection, and their hæmaturia slowly disappears. The country children, on the other hand, develop into peasants who work bare-footed in groups on the constantly irrigated land, where re-infection may often occur.

The ponds (*birket* is the Egyptian name for the village pond), seen in every village in Lower Egypt, require some description for those who do not know the habits of Orientals. To escape from the Nile flood, which occurs every summer, the villages are artificially raised on mounds of earth, and as the country is quite flat there results from this digging a shallow depression, which at the time of inundation is filled with water, and then serves as a bathing-place for children during the hot months. This stagnant pond exists during most of the year, encouraged by the villagers, in spite of all sanitary regulations, because they find it convenient to water their cattle in, and because they employ the shelving banks of the pond to defecate, urinate, and perform their ablutions. Many of them drink water direct from these ponds, but I have already

stated that I do not believe in the introduction of this parasite by the stomach.

**Zoology.**—Cobbold found a *Schistosomum* in a sooty monkey (*Ceropithecus fuliginosus*) from Africa, which died in London in 1857; and though he described it as *Bilharzia magna*, it is now believed to have been a specimen of *Schistosomum hæmatobium*.

Sonsino, in 1876, discovered a similar trematode (*Schistosomum boris*) in the portal vein of a three-year-old bull at Zagazig (Egypt): he found 35 living worms, the female lying in the male gynæcophoric canal, and appearing like a thread of black silk at each extremity. The males were somewhat broader than the human species; the eggs were spindle-shaped, and contained no miracidium. This worm has since been found by Dr. Symmers in cattle from the Sudan, and is said to exist in 75 per cent of the sheep in Sicily.

Mr. Montgomery, a veterinary officer in India, found in 1905 what is, perhaps, a new species, the *Schistosomum indicum*, in one donkey and several horses living in the hills and on the plains. Since then, in a private letter, he states that every careful autopsy upon a horse, sheep, or ox at Lahore shewed adult worms or the long spindle-shaped eggs of this parasite in the rectum or colon. This tends to shew that bilharziasis in animals at least is common in some parts of India.

**Etiology.**—*Age.*—The disease is unknown in infants, but may be found in males at any age from 4 to 70. Three-fourths of the cases which come to Egyptian hospitals are between 15 and 45 years of age.

*Sex.*—It is rare in females, always excepting little girls and peasant women, who, like the men, work bare-legged on the flooded land. In investigating the question of sex, Mr. F. Milton found that out of a total of 1346 hospital cases in Cairo over 94 per cent were males, but that the relative proportion of cases under puberty was 9 males to 1 female, while after the age of puberty there were 20 males to 1 female. This striking difference in ratio can be explained by remembering that when the girls reach puberty they are much more confined to the house, or only work on dry fields, and are thus preserved from the re-infection which attacks males.

*Races.*—All are liable, but Europeans in Egypt rarely contract the disease, excepting a few bare-footed Greeks who lead the same kind of lives as the poorer Egyptians. In South Africa the Colonial and Dutch boys, who paddle and bathe, are by no means exempt, but the disease is extremely rare there in girls, who do not enter the water.

*Occupation.*—In the towns the patients are chiefly children, or adults employed as road labourers and gardeners, while in the country districts the patients are either peasants or ex-peasants. In order to ascertain what proportion of the male population in Egypt suffers from bilharziasis the urine of 100 consecutive patients admitted for all diseases to the medical wards of Kasr el Ainy Hospital was specially examined by the microscope, and no less than 35 were found to pass bilharzia eggs, though only two patients complained of any symptoms of the



disease (F. Milton). In a school of 124 boys near Cairo, 78 per cent had bilharzia eggs in their urine, though they all professed to be perfectly well (Kautsky).

*Climate and Season.*—The land in Lower Egypt is flooded during the late summer and autumn, and probably infection occurs during the early winter months. In the following summer and autumn, after an incubation period of about three months, and some months more for the development of symptoms, patients apply for treatment. The prevalence of the disease in Lower Egypt, as contrasted with Upper Egypt, is probably because the former is supplied with water by irrigation canals practically all the year round, while in Upper Egypt the peasants get water for their crops only at the time of the Nile flood, and therefore have a very much shorter period of time during which infection and re-infection may take place. It is perhaps the absence of a constant water-supply which accounts for the comparative mildness of the disease in South Africa. The disease is presumably limited to warm countries because the miracidium is killed by exposure to cold.

*Varieties of the Disease.*—An analysis of 930 bilharzia cases in one year at Kasr el Ainy Hospital, among both in patients and out-patients, provides the following percentages: bilharzia affecting the bladder alone, 64 per cent, bladder cases complicated by vesical calculus, 14, urinary fistulae, 14; bilharzia of rectum and general bilharziasis, 5 per cent; the remaining 3 per cent were cases in which the patients died of other diseases, but bilharzia worms were found in their portal system.

*Morbid Anatomy.* At an autopsy the infiltration of tissues by the eggs can be best seen in the urethra, bladder, ureters, rectum, and, more rarely, the liver. In the *urethra* there may be small sandy patches due to deposited eggs followed by fibrosis, but the most common lesion is fistula. As regards the origin of the fistula, there is only 1 springing from the floor to 20 arising in the roof or the pubic side of the urethra. It is quite possible to meet with a bilharzial lesion in the glans penis or in the perineum, which may surround the urethra without the urethra itself being primarily affected. In the more common variety of fistula no stricture occurs, though the urethra may be converted into a hard, thick, twisted tube; but a perineal fistula sometimes causes a stricture.

The best known and perhaps most severe lesion is in the *bladder*. Griesinger's original description of which is excellent. The earliest changes in the mucous membrane consist of spots of hyperaemia. There are many small extravasations of blood, the mucous membrane at these places being somewhat swollen and often coated with mucus, which contains quantities of the ova. Sometimes the entire mucous membrane shews marked injection and ecchymoses, but usually the change is limited to small spots of varying size, particularly about the trigone. Later, there may be greyish-yellow, yellowish, or dull white elevations of the mucous membrane, mingled with spots of pigment; or occasionally smooth, leather-like patches beneath the mucous membrane, that look as if they had been steeped in spirits of wine. In other cases the coating is

permeated with urinary salts or a firm sand consisting of eggs or eggshells. It is impossible to remove these patches without peeling off some of the mucous membrane. Occasionally other patches are very soft and friable, and partly mixed with extravasated blood. All these changes are caused by extravasation, inflammation, and fibrosis around the eggs blocking the capillaries. When the blood-supply becomes deficient the patches slough, causing ulcers and crevices.

In other cases, however, the appearances are quite different; for on the mucous membrane there are single or multiple excrescences, varying in size from a pea to a bean, and yellowish in colour, resembling condylomas. As a rule, their condition is such that the mucous membrane over them is unchanged, except that it is somewhat thicker than normal. Occasionally the excrescences are dark red throughout, and the body of the prominence is formed of the swollen submucous tissue, while there are innumerable transitions from flat sessile patches to elevated fungoid protrusions. The protrusions are the result of the living worms, which may sometimes be found *in situ*, whereas the condition I have first described, like most of the pathological appearances, is caused by the eggs.

In the Museum of the Royal College of Surgeons of England there is the best bilharzia specimen I have ever seen of a bladder, taken from a peasant, aged 25, who died in the Alexandria Hospital. The kidneys were large, shewing several cysts, and contained ammoniacal urine, while the pelves and calyces were greatly dilated. The ureters were thickened, and so dilated as to measure, in the collapsed condition, 1.5 cm., but their mucous membrane was intact. The walls of the bladder were 3 cm. thick, and in its cavity there was a calculus the size of a nut, besides two small calculi buried in the thickened walls. A fourth calculus, at the lower end of the left ureter, was discovered at the Museum after I brought the specimen home. Eggs could be found on section almost everywhere in the bladder and ureters.

The pathological changes in the *ureters* are very similar to those in the bladder. Sandy patches may be seen at several spots, but chiefly near the openings of the ureters into the bladder. In old-standing cases annular deposits of eggs may so narrow the calibre of the tube that the finest sound can hardly be passed through it; the natural consequence of which is a dilatation of the upper two-thirds of the ureters, which expand until they resemble a piece of a child's intestine.

Eggs are seldom found in the *kidney*, and the changes in this organ depend chiefly upon the amount of obstruction to the flow of the urine. Especially when a calculus is present, or has been present, the pelvis and calyces gradually stretch until hydronephrosis or pyonephrosis occur, and in the worst cases the kidney is changed into a thin-walled bag of pus.

The *rectum* is sometimes affected when the urinary passages are quite free, and here again the fibrous thickening or the polypoid growths may predominate. But the latter condition is much more common. In early cases there is a general thickening of the mucous membrane, which

is too red in colour and finely granular, bleeding easily, and bathed in mucus, while the sphincter is somewhat relaxed. In advanced cases there are polypoid growths occurring at intervals in the rectum, and extending throughout the whole length of the great intestine. In one case at Kasr el Ainy the lower six inches of the small intestine were also affected.

The *liver* becomes the seat of bilharzial cirrhosis, and its surface presents a peculiar appearance to the naked eye, due to white markings of increased connective tissue shewing through the capsule, and a number of perihepatic nodules projecting from the capsule, of which they are distinct growths. On section, the liver shews an enormous increase of new white fibrous tissue, so that its cut surface looks as if a number of white clay-pipe stems had been thrust at various angles through it. The parenchyma of the liver is homogeneous in appearance, and has a peculiar drab colour which contrasts very markedly with the pinkish-white of the new fibrous tissue. There is no prominence of the hepatic lobules nor retraction of the capsule, as seen in other forms of liver cirrhosis. Microscopically, there is a great increase of the periportal connective tissue of the sublobular and larger portal canals, the fibres of which are mostly wavy and parallel, but here and there arranged concentrically and surrounding ova. The eggs found in the liver consist usually only of the shell with lateral spine; none are seen lying free among the hepatic cells, nor any, usually, in the larger blood-vessels which permeate the new cirrhotic tissue. The whitish nodules on the surface of the liver consist of fibrous tissue containing eggs (Symmers).

The *portal vein* should always be opened to see if it contains any worms. Sometimes none will be found, or only two or three, but at other times each teaspoonful of blood may contain 30 worms, and in one of my cases 436 were found in blood from the liver. The best method of searching for this parasite is to slit open the vein by longitudinal incision, and scoop out the blood with a teaspoon before the liver is removed from the body. The liver can afterwards be cut into small cubes, and washed in saline solution while pressing the cubes with the hands. The worms are easily seen by receiving the blood in a glass dish or a black tray. They may also be found in other veins, such as the inferior vena cava and the common iliac.

Eggs have been found in the *lung* but rarely, for apparently the worms only migrate there when they have lost their way. Dr. Symmers found a pair of living worms, coupled, in the blood of the lung. I have made many unsuccessful attempts to find eggs in the sputa of bilharzia patients.

Fibrous nodules on the outside of the *spleen* have been found to contain eggs, and they have also been seen in the *seminal vesicles* and *prostate*. Eggs, when carefully looked for, have been found several times in the neighbourhood of the *vermiform appendix*, and one case has been reported in which they were confined to this region, being absent from both rectum and bladder. In females between the ages of 10 and 25, the broad

ligament, vulva, vagina, and cervix of the uterus may be affected, as shewn in Figs. 165 and 166. Dr. Symmers found a tumour, about the size of a pigeon's egg, growing in connexion with the ovary and broad ligament of a child four years of age. The tumour consisted of fibrous tissue arranged concentrically round bilharzial eggs or egg-shells. The child shewed no other evidence of bilharziasis. I have only seen one case in which the female urethra was attacked.

Among the rarer sites, living worms, coupled, have been found in the polypoid growths of the rectum, descending colon, and in outgrowths from the intestinal peritoneum. Eggs have occasionally been discovered in the skin, but only in warts on the perineum; sometimes in the mesenteric glands; in the blood of the heart (Griesinger); in the pancreas and in the stomach (Goebel). Mr. F. Milton found them in a case of multiple superficial sinuses in the sacral region of a boy who had apparently no infection in his rectum or bladder, and Dr. Madden has reported bilharzial infection of the omentum and parietal peritoneum.

**Symptoms.** The incubation is uncertain, but seems to vary from three to six months: it is difficult to fix it with any accuracy, for the parasite is sometimes present in the human body for six months or longer without producing any symptoms. Slight hæmaturia is the first sign which attracts the attention of the male patient, but in the girl this symptom may be confused with disordered menstruation. Stains are first noticed on clothes, and then a few drops of blood are passed at the end of urination. This hæmorrhage, with a slight pricking sensation at the prepuce or at the root of the penis, is almost diagnostic of the disease, and is caused by the contracting bladder at the end of urination bursting some of the capillaries filled with the sharp-spined eggs. At an early stage of the disease the urine passed before the final contraction of the bladder is quite normal; but if the after-coming blood be examined, or if the whole of the urine be centrifuged or allowed to stand in a conical vessel, the microscope reveals red blood cells, leucocytes, epithelial cells, and bilharzia eggs entangled in mucus. The hæmaturia is increased after any excess of fatigue, eating, or alcoholic drinking, or after any injury such as a fall. Riding, running, bicycling, and walking long distances are all bad. The individual next finds micturition more frequent, a little backache, and general lassitude, but in countries where the disease is endemic such indistinct symptoms never cause the patients to seek medical advice.

It may again be pointed out that the adult parasites are, so far as we know, harmless in themselves; it is the elimination of the thousands of eggs deposited by each female which produces the symptoms and complications of this disease. The hæmaturia can of course only be caused by deposit of eggs in the mucous membrane of the bladder, while, if the deposit is in the rectum, the symptoms will be mistaken by the patient, and perhaps by the medical attendant, for those of piles or dysentery.

An intelligent patient, on being cross-examined, can generally describe some local pain or discomfort, though the site varies: it is sometimes felt

in the buttocks, the front of the thighs, or the perineum, and in more advanced cases there is generally distinct pain in the inguinal, hypogastric, and sacral regions.

The symptoms of vesical irritation, gradually going on to cystitis, are increasing frequency of micturition, a feeling of not having emptied the bladder, scalding and pain in the perineum and in the lumbar region. Simple cystitis occurs when the mucous membrane of the bladder has become thickened by the deposit of eggs in raised sandy patches with early fibrosis. Infective cystitis is a common complication, being the result of micro-organisms which have been introduced, with or without instruments, from the urethra into the bladder; for when once the bilharzia patches in the bladder have become large, there is no complete contraction of this organ, and therefore the urine constantly dribbles. In the final stages numerous papillomas in the bladder, with sloughing from their ulcerated surfaces, may cause such severe tenesmus that the patient can only get relief by grasping the root of his penis. In adult patients an enlarged prostate adds to all their troubles.

The early symptoms of rectal cases are an increased secretion of mucus and some straining, followed by relaxation of the sphincter and prolapse, due to the formation of papillomas. When the mucous membrane near the sphincter is infiltrated with patches of eggs and fibrosis, the symptoms are sufficiently like chronic dysentery to deceive those unacquainted with the two diseases. In the worst cases, huge polypi are formed with ulcerating sloughs; and the patient, as in cases with similar changes in the bladder, dies, exhausted by pain and constant tenesmus. Stricture never occurs, though there is often great difficulty in defecation.

Letulle has described an instructive case which is worth quoting briefly, because of the oversight in diagnosis. A chemist, aged 68, who had always lived in Martinique, went to Paris, where he contracted pulmonary tuberculosis, for which he was admitted to a hospital in December 1903. It then appeared that for some years he had suffered from a chronic disease of the rectum, characterised by dysenteric diarrhoea and a constant fetid discharge of blood and mucus from the anus. This disease, both in Martinique and in Paris, was diagnosed as an inoperable cancer, because the man was emaciated and cachectic and the lower part of the rectum was extremely hard and immovable. But by some oversight neither the faeces nor the rectal discharge were microscopically examined. One month after admission to the hospital the patient died of exhaustion, and the rectum was found at the autopsy to be the seat of advanced bilharzial infiltration. There was a general hyperplasia of the walls of the whole rectum and lower portion of the descending colon, with some ulceration and a few papillomas. Countless typical eggs and egg-shells were found buried in the muscular coat, and in some instances phagocytes were seen invading the foreign bodies; the Lieberkühn's crypts were double the normal size, and the veins of the submucous tissue were affected by endophlebitis,

but not those of the muscular coat. The bladder, ureters, and prostate were unaffected.

The *vagina* is the part most affected in the female sex, the symptoms



FIG. 165.—Pedunculated labial tumour due to *Schistosomum hominis*. (Madden.)



FIG. 166.—Papilloma of the cervix uteri due to *Schistosomum hominis*. (Madden.)

being first those of subacute vaginitis, the cause of which is usually not recognised, later, the mucous membrane becomes thickened, especially



on the posterior wall, and eventually a growth may protrude from the labia majora not unlike epithelioma in appearance. After the vagina, the vulva and cervix uteri are most likely to be affected in addition to the bladder. Dr. Madden has reported some typical cases in the *Records of the Egyptian Government School of Medicine*, vol. ii (see Figs. 165, 166, p. 876).

Fig. 165 shews a tumour in a girl aged 12, which was said to have been present four years. "It presented an appearance like that of a firm cauliflower mass of venereal warts, and on close examination it was found that the bulk of the tumour was attached by a broad pedicle to the left labium, while a smaller piece was growing from the right labium. The orifice of the urethra, the whole of the vagina and the rectum were quite free from any signs of bilharzial growth, but ova were found in the urine. On taking a small piece of the mass and rubbing the cut surface on a glass slide, eggs were found in the smear. The masses were freely removed by elliptical incisions around their bases, and on cutting through the pedicle of the larger mass several adult bilharzia worms were seen and picked out on the point of a scalpel, while others were present in the subcutaneous fatty tissue beneath the pedicle" (Madden). This is an instance of invasion of the bladder, vulva, and skin, while in another case reported by Dr. Madden the whole vagina was filled with bilharzia papillomas, though the cervix of the uterus was unaffected. It must be remembered that even in cases in which the vulva, vagina, and uterus are all attacked, and where living worms can be picked out of the bilharzia tissue during removal, there may be no eggs in the urine nor other evidence of disease in the bladder.

Fig. 166 represents a bilharzia papilloma growing from the posterior lip of the cervix of the uterus of a comparatively young woman. She had noticed some irritation in the vagina for six years, since the date of her last pregnancy, with occasional discharge of whitish, watery fluid, very often mixed with blood. "On examination a large cauliflower-like growth was seen projecting from the posterior lip of the cervix of the uterus, the base of the mass running up to about the middle of the cervical canal. The uterus was not enlarged, and was freely movable" (Madden).

No clinical symptoms can be referred to bilharzial infection of the lungs or liver, but in Egypt it is recognised that bilharzial cirrhosis can sometimes produce ascites.

*Blood Examination.*—Even after the disease has existed for several years, there is no great anaemia, and if a bilharzia patient is found to be extremely pale it is probable that he is also suffering from ankylostomiasis. The blood of bilharzia patients is found to flow slowly: there is a slight loss of haemoglobin, say to 85 per cent, with a slight decrease of the red cells, perhaps to four millions. Leucocytosis, if present, is caused by the complications of the disease. There is nearly always an increased number of eosinophils, sometimes rising to 52 per cent: the average of several cases was 16 per cent (Kautsky).

*Mortality.* Of 1684 cases treated in the Alexandria Deaconesses' Hospital, 5·8 per cent died.

**Complications.**—The thickened bladder may be so distinct that it can be felt like a small cricket-ball above the pubes, and occasionally hæmorrhage into the bladder may produce a solid clot which blocks up the whole organ, so that a catheter draws nothing off, and, unless relieved by operation, the patient dies.

*Calculi* in the bladder are the best-known sequels, and though opinions differ as to whether bilharzia eggs form a nucleus of some of the calculi, as is sometimes stated, it must be conceded that they are the indirect cause. About 150 patients suffering from stone still come every year to Kasr el Ainy Hospital, and in all of them bilharzia eggs are either still present in the urine or there is a history of recent evidence of the parasite. Moreover, most of these stones have been formed in the bladder, not in the kidney. The few stones that have been examined microscopically have shewn no trace of eggs, but it is quite possible that the stone originates in a slough from the bladder, which may or may not contain eggs. The symptoms of calculus are masked by the cystitis, but the stone greatly aggravates the patient's sufferings, and he gets no relief until lithotrity has been performed. In the later stages of the disease the stones are formed of phosphates, and being soft are not so painful, and are sometimes difficult to diagnose from patches of rough mucous membrane of the bladder encrusted with phosphatic deposit. Though large stones weighing from 20 to 35 ounces are now very rare in Egypt, those still seen occur almost entirely among males, and their geographical distribution corresponds with that of bilharzia disease.

*Urinary fistule*, originating in the roof or the floor of the urethra are another very serious complication among men. In the roof-cases the symptoms are mild until a subcutaneous abscess forms in the perineum from which there discharges a little pus containing eggs. The fistula has now formed, and makes no attempt to heal; it may be recognised by one or more sinuses in the perineum or the posterior part of the scrotum or even on the pubes or the thighs, but always away from the direct line of the urethra. In the floor-cases, which are much more serious, the opening is generally in the perineum; but it may be in the penis, in front of the scrotum, and is always in the direct line of the urethra; the skin is extensively adherent and thickened, and, with the urethra, becomes a sharply defined mass of stony hardness, the meatus being narrow and scarred, with, perhaps, thin, unhealthy pus oozing from it. Many patients do not apply for treatment until an ulcer has formed, followed by a peri-urethral abscess and a stricture. About 18 per cent of bilharzia patients in the surgical wards of a hospital arrive with a fistula in the perineum.

*Fistula in ano* is a rare complication of bilharzia of rectum.

*Carcinoma* is also rare, and it is somewhat surprising that it does not more often develop in the bladder and its neighbourhood.

**Diagnosis.**—The disease in the bladder can be detected by the drop of blood passed at the end of urination, and by the eggs found in the deposit of urine which has been centrifuged or allowed to stand for

a few hours. If no eggs can be found in a suspected case in this way or in the after coming blood, the total quantity of urine passed in the 24 hours must be centrifuged, or a catheter must be passed and the few drops of urine remaining in the instrument examined. The diagnosis between simple cystitis and cystitis complicated by calculus can only be made by examination with the sound. A perimetral abscess due to a fistula in the floor of the urethra may imitate impaction of a calculus in the urethra, but in bilharziasis there is a continuous escape of pus from the meatus; the meatus has a scarred, glazed, narrowed appearance; and the urethra is palpable and very hard all the way from the swelling to the meatus. In case of doubt, a sound must be passed down the urethra. The discharge about the meatus and glans penis is sometimes mistaken for gonorrhœa.

It must always be borne in mind that eggs are sometimes found in the feces though absent from the urine, and I may perhaps be allowed to remind students that in the investigation of tropical diseases the microscopical examination of the feces is quite as important as that of the urine. Rectal tenesmus can be distinguished from symptoms of dysentery by remembering that dysentery comes on suddenly, with diarrhœa, fever, coated tongue, and pain over the descending colon, while in bilharzial proctitis eggs will be found in the blood and mucus passed from the rectum, and, on examination with the finger, a definite, hard roughness or polypoid excrescences can be felt above the sphincter.

Bilharzial cirrhosis cannot be recognised until the ordinary causes of ascites, such as syphilis, alcohol, cancer, malaria, and splenic anaemia are excluded.

In the case of tumours of the female genital organs, it is better to snip off a piece of the growth and search for eggs under the microscope, and so avoid the mistake, which has been made, of treating the growth as an epithelioma.

**Prognosis.** The female worm, during its prolonged period of coupling, is capable of laying an enormous number of eggs, but there is no means of determining how many female worms are present in the body of any given patient. We can only surmise that individuals in Egypt are infested by a much greater number of worms than is the case in South Africa; but definite pathological information on this point is urgently needed from the Cape and other parts of the world. At present we can only assume that the more eggs in the excreta the worse the prognosis. The thoroughly infected Egyptians die a miserable and painful death from exhaustion and debility aided by uræmia from advanced kidney disease. But, on the other hand, I know some educated Egyptians, more than 50 years of age, who state that they have had slight bilharziasis since boyhood without any very ill effects; but as they have always lived in Egypt it is impossible to tell how often they may have been re-infected. Europeans, after leaving Egypt, have been known to pass living eggs in their urine for fourteen years, but their symptoms have not prevented them from doing a fair amount of work (Lortet).

I believe that in most cases of ordinary bilharzia infection the symptoms pass off within four years after leaving the country in which the disease was contracted.

On the other hand, Lawson found blood and bilharzia eggs in the urine of a groom who had contracted the disease in Egypt in 1885, but had not been out of England for the intervening eighteen years. His belated symptoms were apparently caused by some severe riding lessons he had recently taken. It is not stated whether the eggs contained living miracidia. Dr. Guillemard, in his interesting article on this subject in the first edition of this *System* (vol. ii. p. 1100), also writes of a case in England "in which the patient suffered from a severe attack eighteen years from the onset of the disorder, which had been in abeyance for some years."

If we turn for information to the longevity of other endoparasitic trematodes, we find that the overwhelming majority of species live about one year or a little longer, but there are some whose life extends to many years (Braun).

**Treatment.**—No method has as yet been discovered of killing the worms in the human body: the ordinary vermifuges are useless, and no injections into the bladder or rectum have met with success. The liquid extract of male fern, in doses of 15 minims three times a day, is the only drug of known value, for, though it does not expel the parasites, it seems to weaken their power of doing harm: it diminishes hæmaturia, allays vesical irritation, and reduces the number of eggs passed in the urine and fæces. But it must not be continued for more than two weeks at a time, or toxic symptoms may occur, such as giddiness, headache, pain in the eyes and epigastrium, singing in the ears, and vomiting, all of which symptoms I have observed. With the exception of this empiric remedy, we must be content to treat the disease symptomatically.

Methylene blue, 3 grains in a capsule given once or twice a week, is of no curative value, but is sometimes useful as an analgesic for great tenesmus; in advanced cases it may be given to test the efficiency of the excretory powers of the kidneys (renal permeability).

Hæmostatic injections for hæmaturia are unscientific and dangerous and must never be employed, but early cystitis is benefited by washing out the bladder with boracic acid or boroglyceride. Salol, benzoic acid, urotropin (15 grains t.d. in plenty of water), and helmitol (15 grains t.d.) are all of use in cystitis. Rectal cases can be treated with suppositories of belladonna, or with enemas of starch and opium or of sulphate of copper. Enemas of infusion of quassia have been recommended in order to get the worms away from the papillomas. The rectal tenesmus is almost entirely caused by bilharzial growths, fibrous or polypoid, in the neighbourhood of the sphincters, so that much temporary relief can be given by cutting away the mucous membrane above the anus and stretching the sphincters, after which it is advisable to dab the wound with a solution of chloride of zinc (1 in 10) and then wash it thoroughly with saline solution. Severe cases of prolapse should be treated by lineal

cautery, and, if that fail, by excision, if possible preserving the sphincters. Growths from the female genital organs should be excised. The treatment of complications is purely surgical, and for that I must refer readers to Mr. F. Milton's various papers.

**Prevention.**—Until the way in which the parasite gains entry into the human body is certainly established, it is impossible to legislate on this subject; but enough has been said to shew that bathing or paddling in infected and stagnant water is more dangerous than drinking muddy, unfiltered water, or eating salads and uncooked vegetables. Patients should be compelled to evacuate their excreta into dry earth or sand, in which the miracidia cannot hatch, and not into water, which is the favourable medium for development. Miracidia are most surely prevented from hatching by formalin (1:160), less efficiently by perchloride of mercury (1:1000), or carbolic acid (1:20). Should an imported case be introduced into a tropical country where the disease is unknown, and where conditions for its spread are favourable, the greatest care must be taken to keep the fæces or urine of the patient dry and away from water, in order to prevent diffusion of the infection.

**Schistosomum japonicum** Katsurada 1904.—(Synonym: *Schistosoma cattoi* Blanchard 1904.)—In April 1904 this worm was discovered by Professor Katsurada, of Okayama, and independently a little later by Dr. Catto, in sections from a fibrous growth near the vermiform appendix of a Chinaman (from Fukien) who died of cholera at Singapore. For some years the Japanese physicians had observed in the provinces of Yamanashi, Hiroshima (Central Japan), and Saga (in Kiushu, North-West Island) a strange endemic disease characterised by enlargement of the liver and spleen, cachexia, ascites, and diarrhoea, with a discharge of mucus and blood. At the autopsy of such cases, eggs of an unknown worm were found in the liver and some other organs. Katsurada was struck with the resemblance of the egg, containing a miracidium, to that of *Schistosomum hematobium*, and determined to examine the cats and dogs of the endemic areas, because he had already found that some trematodes infecting man were also present in dogs and cats. In two cats from Yamanashi he found many of these worms in the portal and mesenteric veins, besides eggs in the liver and the walls of the large intestine. He also had the opportunity of studying twelve human cases, and in the fæces of five of them he found the eggs; he also found eggs in three cases in the liver, and in one case in the large intestine, but never in the bladder. Dr. Stiles, of Washington, writes to me that he has seen *Schistosomum japonicum* in a case from China and in another from the Philippines. This parasite in Asia, therefore, seems to be the analogue of the original *Schistosomum* of Africa, but, curiously enough, does not seem to affect the urinary passages. In Dr. Catto's case the bladder was thickened where adhesions had formed with the rectum, but with this exception the organ, including its mucous membrane, was quite healthy.

The distinctive characteristics of this new trematode, as compared



with the older variety, are its smaller dimensions, the larger size of its posterior sucker as compared with the anterior sucker, the smooth surface of the body of the male worm, which is quite devoid of tubercles, the eggs, which are destitute of spines; and the fact that it infects cats in Japan. According to Katsurada, the average measurement of eight males is 10.13 mm., his specimens from cats varying from 7 to 12 mm. Only a few females were found uninjured, measuring from 8 to 12 mm. He thinks that the worm when inhabiting man ought to grow for a longer time, and therefore should be larger. Dr. Catto is unable to decide whether the adult worms occupy the arteries or the veins, but believes that they occur in both. The eggs (Fig. 167) are oval, measur-

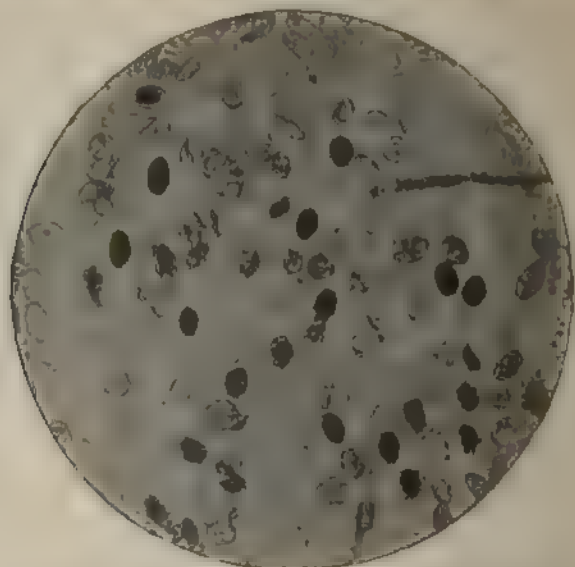


FIG. 167. Eggs seen in section of *Thinina* serratiform appendix (Catto).

ing between 0.06 and 0.09 mm. in length and 0.03 to 0.05 mm. in breadth. They have a stout, smooth shell without any trace of a spine, and in the cases reported by Katsurada and Bayer (from China) the ovum contained a miracidium. In Dr. Catto's case the eggs of the worm were found chiefly in the intestinal tract and its appendages, inhabiting the gut from the cæcum to the anus in two layers—the one subperitoneal, where the eggs were scarce; the other in the submucous coat, where they were very numerous. The rectum and appendix contained the greatest number of eggs, while they were numerous in the liver, lying singly or in clusters embedded in the thickened fibrous connective tissue. He also found eggs in the enlarged mesenteric glands, in the outer wall of the gall bladder, in the pancreas, in the capsule of the liver, and in the fibrous coat of the larger mesenteric vessels. Now that this parasite has



been definitely described, more information as to the symptoms it causes will probably be forthcoming, and from their investigation advances may possibly be made in the cure of patients with bilharziasis.

F. M. SANDWITH.

## PHYLUM II.—Nemathelminthes

By Sir PATRICK MANSON, K.C.M.G., M.D., F.R.S., and A. E. SHIPLEY, M.A., F.R.S.

### CLASS I.—NEMATODA

The nematodes are long, slender, cylindrical animals with bodies which taper towards both ends, at one of which—the anterior—is placed the mouth; at or near the other—the posterior—the anus.

They are covered with a cuticle, often transversely striated and

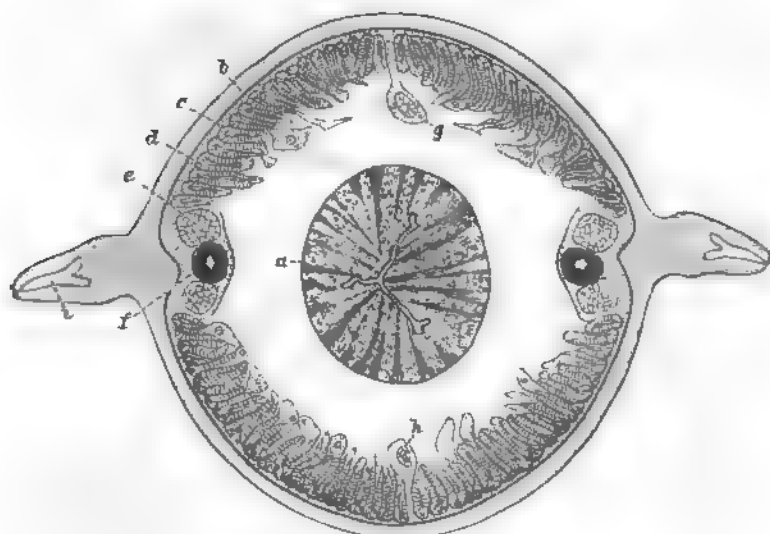


FIG. 1188.—A transverse section through the body of *Ascaris transfuga* Lind. in the region of the oesophagus. *a*, the buccular oesophagus with its irradiate lumen; *b*, the cuticle; *c*, the sub-cuticle; *d*, the muscular layer; *e*, the lateral nerve running in the lateral line; *f*, the excretory canal; *g*, the dorsal, and *h*, the ventral nerve; *i*, the tricolpate rod in the tail.

sometimes consisting of several layers. The cuticle is shed from time to time, as a caterpillar sheds its skin, and it plays an important part in the economy of the roundworms. Beneath the cuticle is a nucleated syncytium, and beneath this again a muscular layer. These three layers form a body-wall, which encloses a body-cavity, in which lie the long straight alimentary canal, and the long and usually much convoluted ovary, uterus, and in the male the testis.

The mouth is sometimes provided with papillae, sometimes with hooks;

sometimes it is simple. The short œsophagus is generally marked off from the intestine by a constriction, or by a bulb. In some forms the alimentary canal is aborted in certain stages.

The female organs of generation consist of a pair of tubes, rarely of one tube only, at the upper end of which—the ovarian tubules—the ova originate; lower down fecundation is effected; lower still the ova are provided with yolk and vitelline membrane, and assume their characteristic appearance. The two uterine tubes unite to form a short vagina which opens on the ventral surface, usually about the junction of the anterior third of the body with the posterior two-thirds, more rarely posteriorly.

The male nematodes, readily recognised by their inferior size and often by their strongly curved tails, have but a single testis, a long tube filled with non-flagellated spermatozoa. This opens by a vas deferens into the terminal portion of the intestine—the cloaca. In the walls of the cloaca, lodged in an invagination, are usually one or two spicula—long chitinous rods which can be protracted or retracted; these are used during copulation. In certain families the tail of the male is winged, in others it is expanded into a sort of umbrella-shaped bursa, in others, again, it is simple in structure; it is also provided, both in front of and behind the anus, with a number of papillæ. These characters of the tail form valuable criteria for determining species.

Excretion is carried on by two vessels which course along the sides of the body—one on each side—in what is known as “the lateral lines.” These lines are narrow, longitudinal thickenings of the syncytial ectoderm where the muscular part of the body-wall is absent. The two vessels they include unite anteriorly and open by a transverse slit—the excretory pore—on the ventral surface. Round the œsophagus there is a nerve-ring which gives off longitudinal cords, the two chief lying in the mid-dorsal and mid-ventral line.

Unlike what occurs in the cestodes and usually in trematodes, the sexes in the nematodes are, with few exceptions, separate.

Usually oviparous, not a few are viviparous or ovo-viviparous. The embryo is a long, slender, cylindrical, eel-shaped organism which, while *in ovo*, is coiled up, but when free is outstretched and exhibits active movement. Sometimes it gains access to its definitive host directly; usually, however, it has first to pass through a metamorphosis in an intermediate host. Certain species possess what is known as the “free rhabditis form,” which lives in the earth or mud. These are called heterogamous; that is, they present a form of alternation of generations in which both stages are sexual but differ in character, i.e. one may be parthenogenetic and one bisexual.

### Family I.—Ascaridæ

The members of this family of nematodes are characterised by their comparatively stout bodies, and by the possession of three well-marked

lips carrying papillæ—one lip being dorsal, the other two being ventral and meeting in the middle line. The œsophagus has a bulb. The ovary is paired. Oviparous; the development is direct. The tail of the male is strongly curved and carries one or two spicules. Four species are parasitic in man, and all of them in the intestine.

i. *Ascaris lumbricoides* L. 1758 (Fig. 169) ("The Round Worm"), whose usual and normal habitat is the upper part of the small intestine, is, with one rare exception, the largest of the nematodes parasitic in man. The male worm measures 15 to 25 cm. in length by about 3 mm. in breadth; the female 20 to 40 cm. by 5 mm. Both are cylindrical in shape, and taper to the ends, particularly towards the head. Close to the tail the body is somewhat flattened in a ventro-dorsal direction. In colour they are grey or pinkish; to the touch they are firm and stiff. The surface is glistening and polished, and is marked by fine, closely-set, transverse ridges. The musculo-cutaneous body-wall is so transparent that the coils of the long uterine or testicular structures can be discerned through it in many places. The tail of the female, close to the tip of which opens the two-lipped, transversely disposed, slit-like anus, is straight. That of the male is strongly curved in a ventral direction, two spicules usually protruding from the subterminal cloaca. On the ventral surface of the tail, and extending as far as the curve extends, some 70 to 75 minute papillæ are arranged on each side of the middle line. Of these seven pairs are post-anal. The two much convoluted uterine tubes are of great length—ten to fifteen times that of the worm—and occupy the posterior two-thirds of the body. They unite to form a short vagina which opens ventrally some distance behind the head. The excretory canals, lying in the lateral lines, unite and open a short distance behind the mouth. The three papillæ-bearing lips characteristic of the family are very well marked.

The ova (0·05 to 0·07 mm. by 0·04 to 0·05 mm.), of which the uterine tubes contain many millions, are ovoid, spherical, or sometimes barrel-shaped. They have a rough mammillated surface, a multiple outline, and granular contents. White while in the uterus of the worm, they are stained brown by the bile on entering the intestine of the host. At birth, and for a long time afterwards, they exhibit no sign of the embryo; but if kept in water, in the light, and at a summer temperature, an embryo of the usual nematode character is developed in the course of five or six months. Some experimentalists state that during the heats of summer the embryo may be developed in a couple of weeks. Desiccation in summer and freezing in winter suspend development, but kill neither ovum nor embryo. When fully developed the embryo still remains in the egg and does not seek to escape spontaneously. It will remain alive under suitable conditions for upwards of five years. On the ovum being swallowed by the definitive host, the embryo speedily breaks through the shell and advances so rapidly in development that at the end of a month it is a sexually mature animal giving birth to crowds of ova. These facts have been proved by carefully conducted feeding experiments. Von



FIG. 14. — *Caenorhabditis elegans* (Trembley).

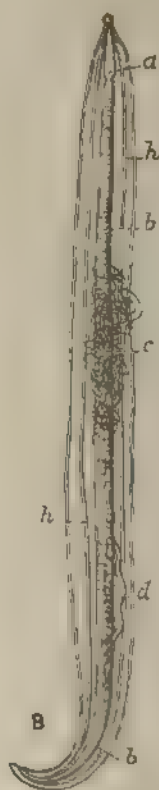


FIG. 17. — *Ascaris megalocephala* (Trembley).   
 a, anterior end;   
 b, uterus;   
 c, pharynx;   
 d, intestine;   
 e, posterior end;   
 h, lateral excretory canals.



FIG. 18. — *Ascaris megalocephala* (Trembley).   
 a, anterior end;   
 b, uterus;   
 c, pharynx;   
 d, intestine;   
 e, rectum;   
 f, anal opening;   
 g, posterior end;   
 h, lateral excretory canals.

Linstow's suggestion, that a certain myriapod—*Iulus guttulatus*—acted the part of intermediate host, seems therefore to be superfluous.

*Ascaris lumbricoides* is cosmopolitan, being found in all countries from the arctic circles to the tropics. In a general way it may be said to be much more common in the tropics than in cooler latitudes; a great deal depends, of course, on local conditions, particularly on the character of the water and vegetable supplies, and their liability to contamination by faecal matter containing the ova of the parasite. As a rule, it is more frequent in the country than in towns, in children and young people than in adults or infants. It has been found, however, in infants only 11 weeks old, and in old men up to 78. Lunatics, doubtless from their careless or filthy habits, are particularly subject to ascariides.

In temperate climates one, two, or up to ten may be found together in one host; but in the tropics twenty or thirty are not uncommon, and instances of hundreds being found in the same patient are far from

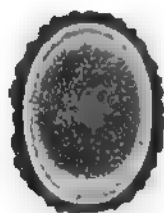


FIG. 172.—Egg of *Ascaris lumbricoides* ( $\times$  about 400). Normal. Light to dark yellow in colour. From LANGE.

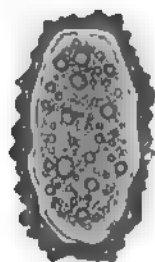


FIG. 173.—Egg of *Ascaris lumbricoides* ( $\times$  about 400). Abnormal. Yellow to brown. From LANGE.

rare. Perhaps the most remarkable case on record is one published by Fauconneau-Dufresne, in which a boy of 12 passed over 5000 worms in less than three years—most of them by vomiting; 600 were got rid of in a single day.

Although the small intestine is the usual seat of these worms, not infrequently they wander downwards into the large intestine or upwards into the stomach, and so into the œsophagus, and out by the mouth or nostrils. They have even caused death from suffocation by creeping into the glottis. Cases are on record in which they had entered the Eustachian tubes or the nasal ducts, finding their way to the outside by the external ear in the one case, or by the canaliculi lacrimales in the other. A more frequent occurrence is their impaction in the biliary or pancreatic ducts; in these situations sometimes several worms have been found together. Thus located they may give rise to grave symptoms from blocking and dilatation of the ducts; even abscess of the liver has resulted from such an invasion. In other cases, by perforating the intestine round worms may escape into the peritoneal cavity, setting up peritonitis; more especially if some of the intestinal contents escape along

with the worms. In some instances peritonitis has not ensued; in the latter cases, and also in many of the cases in which these worms were found at the post-mortem examination in the air-passages, it is not improbable that the wandering did not take place till after the death of the host. This post-mortem wandering may be correlated to the curious fact that in acute disease, and as death approaches, round worms often exhibit a disposition to quit the patient's body. There have been many instances of verminous abscess recorded, particularly as affecting the umbilical region in children and the groin in adults, which were most probably connected with the imprisonment of ascarides in hernial protrusions of the bowel. The kidney, spleen, pleura, and the urinary passages have sheltered strayed specimens of these parasites at times; they have even escaped by the urethra.

*Symptoms.*—From the fact that in many countries scarcely an individual up to middle life is free from this parasite, it is manifest that *Ascaris lumbricoides* does not necessarily or usually give rise to important pathological conditions. Nevertheless, there are good grounds for believing that at times, particularly in young children and in others with sensitive nervous systems, it is really a cause of more or less grave reflex or direct disturbance. Thus, it appears to be an occasional excitant of convulsive seizures; of perversions of the senses of sight, smell, hearing, and taste; of vertigo, hysteria, mental disturbances, dreams, and so forth: at all events, in many such cases these morbid symptoms have disappeared on removal of the parasites. Such direct effects of its presence in the alimentary canal as dyspepsia, griping pains, nausea, vomiting, irregular action of the bowels, mucous, membranous, or bloody stools, excessive, defective, or perverted appetite, itching of the nose or anus, malnutrition and anæmia, are very common in association with this parasite; they subside at once on the successful action of an anthelmintic.

The report of the Jenner Hospital at Berne (1890) includes the account of a case in which *As. lumbricoides* was present in large numbers. The blood shewed, before the expulsion of the worms by *santonin*, 2,480,000 red cells, while two weeks afterwards the red cells had risen to 4,200,000 per c.mm. The blood often also shews an eosinophilia of greater or less extent: Solley reports 33 per cent in one case, Boycott 24 per cent and 25 per cent respectively in two other cases. Cases shewing no marked increase of these cells are, however, quite common.

*Diagnosis.*—Failing the spontaneous discharge of the nematode in the stools or in vomited matters, a dose of *santonin* will quickly confirm or negative any suspicion of their presence. When it is deemed inadvisable to give this drug on bare suspicion, a microscopic examination of the stools will clear up the diagnosis at once. In cases of *ascaris* infection the number of ova is so prodigious that the minutest portion of *fæces* is nearly sure to contain several specimens. To examine it, all that is necessary is to express a small portion, not larger than a big pin's head, if necessary moistened with a little water, between a cover-glass and slip, and to search every



part of it with a magnifying power of something under 100 diameters. If the stools be fluid they should be allowed to stand, and the sediment then examined.

*Treatment* — Round worms are got rid of at once by the administration of *santonin*. It is best to combine it with a purgative. A few grains of calomel or a dose of castor oil suffice. A good plan is to give half a grain to four grains, according to the age of the patient, for three successive nights at bed time, and on the mornings following the first and third doses to exhibit a dose of castor oil. In the tropics, and in countries in which the parasite is particularly prevalent, such a course of *santonin* may be administered to children twice a year with great advantage to their general health. When prescribing *santonin* the physician should warn the patient, or, in the case of a child, the attendants, of the effect of this drug in causing temporary discoloration of the urine — a greenish-yellow tint in acid, a red or purple tint in alkaline urine. He should also inform them of the effect on vision, objects appearing some hours after the dose of a blue and, later, of a yellow colour; and, perhaps, finally, temporary loss of colour vision. Rarely does a medicinal dose give rise to serious toxic symptoms such as aphasia, tremors, hallucinations, convulsions, enfeebled respiration, slowing of the pulse. Sometimes, however, these symptoms of intoxication occur after *santonin*: in particular idiosyncrasies unnecessarily large doses must therefore be avoided.

It is manifest, from what has been said about the life-history of the parasite, that a pure water-supply is the best prophylactic. Where this cannot be secured all drinking-water should be boiled. Similarly, wherever the nature of the fertilisers employed by market gardeners is not beyond suspicion, all vegetables should be cooked or well-washed in boiled water.

ii *Ascaris canis* (Werner) 1782. — (Synonyms: *Lumbricus canis* Werner 1782, *As. levis* Goeze 1782, *As. cati* et *canicula* Schrank 1788, *As. canis* et *felis* Gmelin 1789, *As. tricuspidata* et *felis* Bruguiere 1791, *As. icterici* Rud 1793, *Fusaria mystax* Zeder 1800, *As. marginata* et *mystax* Rud. 1802, *As. alata* Bellingham 1839) (Fig. 174). — Normally parasitic in dogs, cats, and some other carnivora, this species is sometimes found in man. It can be readily recognised by its relatively small size (male 40 to 60 mm. long, by 1 mm. in diameter; female 120 to 180 mm., by 1·7 mm.), by the two very conspicuous cutaneous wings,<sup>1</sup> projecting from each side of the head in both sexes, giving the head end an arrow head appearance, and by



FIG. 174. — *Ascaris canis*.

Similar "wings" are seen in section in Fig. 168

the number and arrangement of the twenty pairs of pre-anal and five pairs of post-anal papillæ on the tail of the male. The ova (0.068 by 0.072 mm.) are covered with a beautiful network resembling the mace on a nutmeg. The parasite gains entrance to the body of its host in the same way as in the case of *As. lumbricoides*.

iii. *Ascaris maritima* Leuckart 1876.—An immature female, 43

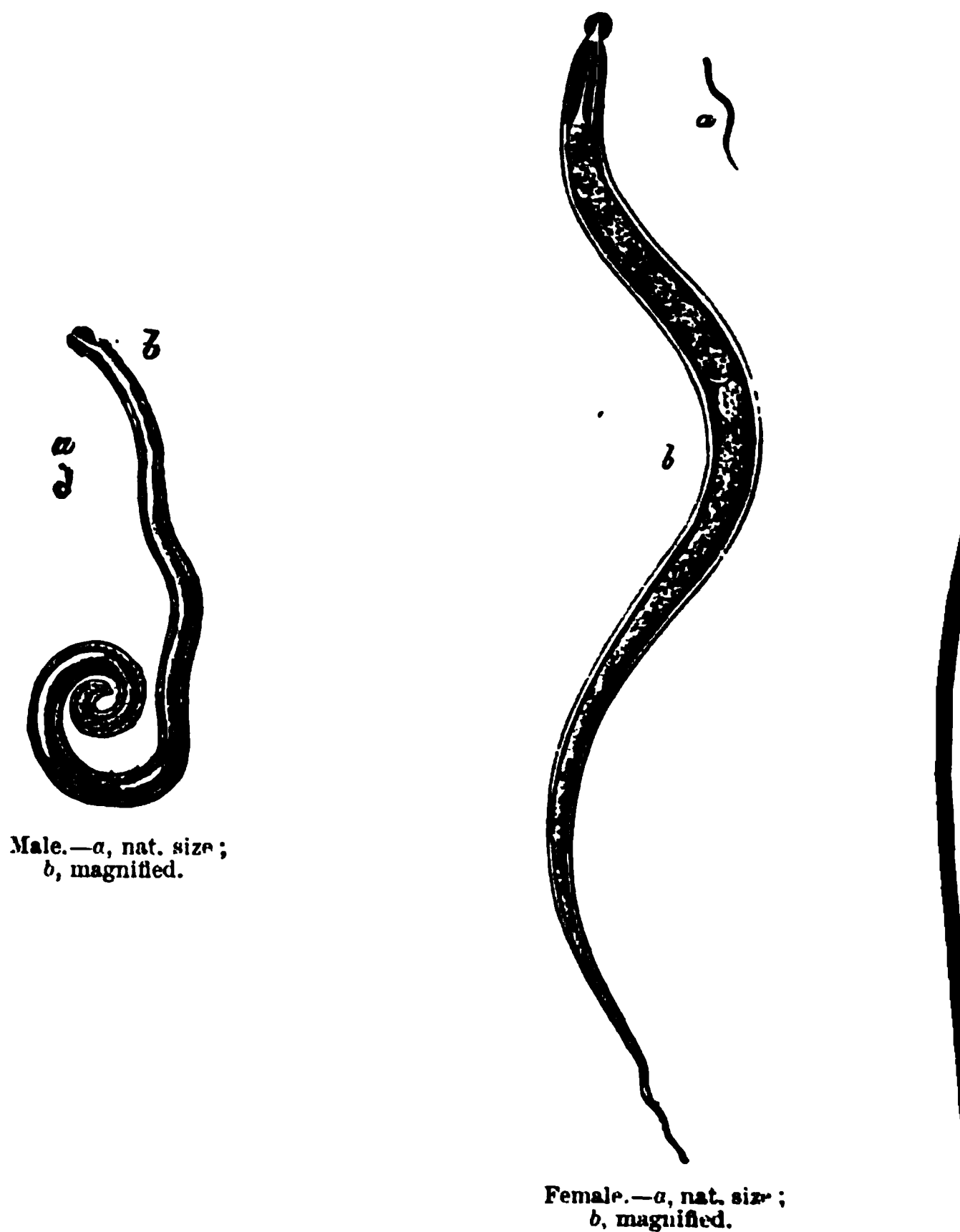


FIG. 175.—*Oxyuris vermicularis*.

mm. long and 1 mm. broad, was vomited by a child in Greenland in 1865. Probably this was not a normal human parasite, but accidentally introduced. It is, in Leuckart's opinion, nearly related to the *As. transtent* of the bear.

iv. *Oxyuris vermicularis* L. 1767.—(Synonyms: *As. vermicularis* L., *Fusaria vermicularis* Zeder 1803) (Fig. 175).—The "Thread worm" or "Seat worm," like *A. lumbricoides*, is a very common parasite, and is

in all countries. Like the round worm it has a predilection for children and young people, in whose fæces the worms are by no means absent, looking like minute (9 to 12 mm. long by 0·4 to 0·6 mm. broad), white, slowly moving, short pieces of fine thread. These are female oxyurides. The male worms, which are both fewer in number and very much smaller (3 to 5 mm., by 0·16 to 0·20 mm.), are hard to find in the stools or intestinal mucus without the aid of a lens. They are further distinguished by their tails—that of the female being tapering, and pointed, the anus opening at its base; the vagina on the ventral surface a little in front of the middle. In the male the tail is abruptly truncated; usually, particularly after death, it is curled up into a sort of spiral; the cloaca is terminal and contains only a single spicule; the tail is further distinguished by six pairs of ventrally placed papillæ, of which the anterior and the posterior pairs are the largest. In both sexes the head end is very much thickened, and carries on its upper and under aspects a double cuticular sac filled with clear fluid. Viewed in profile this double sac gives the head an appearance which is very aptly compared by Blanchard to the amber mouth-piece of a Turkish tobacco-pipe.

The eggs (0·05 by 0·016 to 0·024 mm.) are oval, much flatter on one side than on the other. Their shell consists of three layers, except at one point on the dorsal surface where the middle layer is defective. It is at this point that the embryo subsequently effects its escape.

At the time the egg leaves the parent worm the embryo, though visible, has not quite completed its development. So soon, however, as the ovum enters the fæces, whether inside or outside the host, progress is rapid; but until transferred to the human stomach the development of the embryo does not advance beyond a certain point, the little animal always remaining a prisoner in the shell. Under suitable conditions it remains alive in this state for days or weeks. Long immersion in water is said to kill it; consequently, we may infer that the drinking-water is not a usual medium of infection with oxyurides. An intermediate host is not required. The ova gain access to the human stomach on fruit, raw vegetables, in dust, by being conveyed on dirty fingers to the mouth, and probably in many other and similar ways. When ova or pregnant oxyurides are swallowed experimentally, mature worms appear in the fæces at the end of two or three weeks. Grassi, after swallowing six female oxyurides, found their progeny in his stools at the end of fifteen days; and they continued to appear in every stool for over a month. From the latter circumstance it is evident that development does not proceed in all the ova, nor probably in all the worms, at the same rate.

It is believed that on the egg being swallowed the embryo is liberated in the stomach; it then passes into the small intestine, where, after undergoing a succession of moultings, it attains sexual maturity and impregna-



FIG. 176. — Egg of *Oxyuris vermicularis* (x about 400). Almost colourless. From LOOSS.

tion is effected. The male worm usually dies after this event, passing out in the fæces; but the impregnated female migrates to the cæcum, where she remains till her ova are matured. She then descends to the rectum, where part of her ova are probably expelled, she herself perhaps passing out along with them in the fæces. Other worms escape spontaneously by wriggling through the anus, and, doubtless aided by the scratching and manipulation their presence occasions, spread over the neighbouring integument, and even wander into the vagina, urethra, or prepuce. Thus they scatter their eggs about, and by their movements cause intolerable itching. The warmth of bed seems to provoke this exodus of oxyurides: for it is usually in bed that the characteristic migration and attendant irritation set in, phenomena which recur with remarkable regularity at the same hour every evening.

The irritation secures by auto-infection the continuation of the race of animals producing it. By the scratching that ensues, the wandering worms are broken up, and their eggs, and even fragments of the worms themselves, are smeared over the fingers, forced under the nails, and spread about the body. In this way the eggs are inadvertently conveyed to the mouth of the host, to be swallowed and so to start a fresh generation of parasites. The itching of the nose, which is so frequent a concomitant of rectal and intestinal irritation, and such habits, so common in children, as sucking the thumbs during sleep and biting the nails, contribute to ensure this result. In this way patients keep up their stock of parasites for many years, and often into adult life. In some instances the intestines have been so loaded with these worms that the mucous membrane looked as if covered with a pile like velvet. Usually infection does not proceed to this degree; but thousands of worms are often present in the bowel, agglutinated by the mucus into masses and balls.

*Symptoms.*—In consequence of the nocturnal wanderings of the worms and the intense irritation they give rise to, local symptoms, such as mucoid and bloody stools, morbid sexual excitement leading to masturbation, seminal emissions or enuresis, eczematous conditions about the anus, and pains resembling those of stone in the bladder, are common. Reflex disturbances may also occur, such as hysteria, convulsions, chorea, perversions of appetite, anæmia, and similar consequences of prolonged intestinal irritation. In the presence of such symptoms the appearance of worms or ova in the stools at once establishes the diagnosis.

The eosinophil cells of the blood are frequently slightly increased in number—Dr. Boycott states that in about two-fifths of his cases in children who harboured *Oxyuris*, a definite increase in the eosinophils had occurred;—more rarely a high grade of eosinophilia (up to 16 per cent) is set up, whilst quite commonly the blood shews normal proportions.

*Treatment.*—The facts of the life-history of the parasite, as just set forth, must be borne in mind in directing treatment. Grassi's experiment has shewn that the parasites may continue to arrive at maturity in successive swarms during the last four or five of the six or seven weeks following a single infection. Consequently, treatment to be radical must

extend over this period at least. Moreover, measures must be taken to prevent auto-infection. With this latter object in view, in the case of a child care should be taken that the buttocks are covered with stout drawers during sleep; or a long night-dress should be tied beyond the feet, or some such device employed so as to make it impossible for the child to soil its fingers with the ova of such worms as may creep out from the anus during the night. It is a good plan to cover the hands with gloves. Finger-nails must be kept short and clean, and thumb-sucking and nail-biting discouraged. An affected child should sleep by itself, so as to minimise the risk of spreading the complaint. An occasional aperient had better be administered during treatment. Every night for a time, and later every second or third night, an anthelmintic enema must be administered. There are many efficient drugs which may be employed in this way. Salt and water, an ounce to the pint, infusion of quassia, a few drops of tincture of the perchloride of iron, vinegar or alcohol and water, and lime water may be mentioned. As it is hopeless to reach the cæcum, where the bulk of the worms is situated, by enemas, such means are of use in killing or dislodging those parasites only which have descended to the rectum prior to their escape per anum; the enema, therefore, need not exceed a pint in the adult or five ounces in the child. Suppositories of quassia with cacao butter are said to be an efficient and convenient substitute. If precautions are effectually taken against reinfection from without, and auto-inoculation, the worms disappear rapidly; and a radical cure may be looked for in from four to six weeks. Nocturnal irritation is prevented by smearing the neighbourhood of the anus with weak mercurial ointment, or sponging with carbolic lotion.

In families and large public institutions in which this helminthiasis has broken out some trouble should be taken to prevent its spread. Particular care should be exercised to secure clean underclothing, clean bed-linen, clean towels, and clean privies; raw fruit and vegetables should be interdicted, and all plates, dishes, and drinking-vessels so cared for that such dust or dirt as might possibly contain ova of the parasite is prevented from contaminating them.

## Family II.—Strongylidæ

In the *Strongylidæ* the male opening is placed at the posterior end of the body, at the bottom of an umbrella- or bell-shaped copulatory bursa, the margin of which is furnished with a varying number of papillæ. There are six mouth-papillæ, and often chitinous teeth. Body generally cylindrical, not filiform.

i. *Eustrongylus gigas*<sup>1</sup> (Rudolphi) 1802.—(Synonyms: *As. canis et martis* Schrank 1788, *As. visceralis et renalis* Gmel. 1789, *Strongylus gigas* Rud. 1802, *Eustrongylus gigas* Dies. 1851, *Strongylus renalis* Moq.-Tand. 1860, *Eustrongylus visceralis* Raill. 1885.)—The giant strongyle, the largest of the nematodes affecting man, is much more frequently

<sup>1</sup> Ward describes this species under the name *Diocetophyme renale* Goeze 1782.

found (although even in them it is a very uncommon parasite) in certain other mammalia—particularly, according to Leuckart, in those that are always or occasionally ichthyophagous, such as the dog, wolf, fox, and seal. It has also been found in the ox and horse, which, as is well known, in northern latitudes sometimes eat fish. It is conjectured that certain larval nematodes of the muscles of fish are an early stage of this parasite; experiment has not confirmed this conjecture.

In appearance the giant strongyle is like an overgrown *A. lumbricoides*; it is readily distinguished, however, from this parasite by its enormous size, and by the copulatory bursa on the tail of the male, which is so large as to be quite apparent to the naked eye; further, it is blood red. The male measures from 14 to 40 c.m. in length by 4 to 6 mm. in breadth; the female 25 c.m. to 1 metre in length by 4·5 to 12 mm. in diameter. The male has only one spicule, which protrudes from the cloaca at the bottom of the copulatory bursa. The eggs are oval (0·064 mm. to 0·068 mm. by 0·042 to 0·044 mm.), and have a thick, brown, fragile, foveolated shell which is quite characteristic and constitutes an important diagnostic indication if met with in bloody urine.

The parasite is usually located in the kidney. Two or three or more may be found together; in rare cases even as many as eight. Sometimes it appears to cause little damage and few symptoms; more usually it causes disorganisation of the organ, converting it into a pus-filled cyst, and giving rise to much pain and hæmaturia. It may leave the kidney and stray to the peritoneal cavity, to the pleura, to the liver, bladder, perinephric fascia, and other parts, in which situations it has been occasionally encountered in the lower animals. Although it has only been found some twelve times in man, it has a wide geographical distribution, having been met with in the lower animals in most countries of Europe, and of North and South America.

Should the characteristic ova be found in the urine, and local pain determine the kidney in which it is lodged, the parasite might be removed by surgical means.

ii. **Strongylus apri** (Gmelin) 1789.—(Synonyms: *Gordius pulmonalis apri* Ebel 1777, *As. apri* Gmel. 1789, *Strongylus suis* Rud. 1809, *St. paradoxus* Mehlis 1831, *St. elongatus* Duj. 1845, *St. longerragrinatus* Dies. 1851.)—This parasite has been found, in large numbers, in the lungs of a boy in Transylvania, and in the alimentary canal of man. The males measured 12 to 25 mm. in length by 0·55 in diameter, the females 26 to 50 mm. by 0·7. This species normally occurs in the bronchi, usually the smaller bronchi, in the pig, both domesticated and wild.

iii. **Strongylus subtilis**<sup>1</sup> Looss 1895.—The males are 4 to 5 mm. long, anteriorly only 0·009 mm., but just before the bursa 0·07 mm. in breadth. The male has a single spicula. The females are 5·6 to 7 mm. in length, and anteriorly 0·01, widening to 0·097 behind. The ripe eggs are oval.

<sup>1</sup> Looss (324A) has recently redescribed this worm under the name *Trichostrongylus subtilis* (Looss). He mentions two other species of the same genus, *T. probolurus* (Railliet) and *T. citrinus* Looss, also found in sheep and camels, as occasionally met with in man.



0.063 by 0.041 mm. in size, and thin-shelled. It occurs in the alimentary canal of man, in Egypt and Japan, and is also met with in camels and sheep.

iv. *Ankylostoma duodenale*<sup>1</sup> Dubini 1843.—(Synonyms: *Strongylus quadridentatus* v. Sieb. 1851, *Dochmius anchylostomum* Molin 1860, *Sclerostoma duodenale* Cobb. 1864, *Str. duodenalis* Schneid. 1866, *Dochmius duodenalis* Lekt. 1876) (Figs. 178 to 184).—Since Dubini discovered the tunnel-worm in Milan in 1838 it has been found in so many countries that it is highly probable that *A. duodenale* is generally endemic all over the globe between the parallels 51° 31' N. and 30° S.; at all events, in those localities where the character and hydraulic conditions of the soil and the habits of the inhabitants favour its propagation. In Egypt it is found in about 20 to 30 per cent of autopsies; in India, Dobson found it in the stools of 75.58 per cent of 1249 natives to whom he had administered thymol.



FIG. 177.—Egg of *Strongylus edentatus* ( $\times$  about 400). Colourless. From Looss.



FIG. 178.—To the left, a male and female *Ankylostoma duodenale*; and to the right, male and female *Necator americanus*, in copula (about life size). From Looss.



FIG. 179.—*Ankylostoma duodenale* (nat. size). After Schultze.

It seems to be equally common in the West Indies, Guiana, Brazil, Ceylon, the Straits Settlements, Java, China, the Philippines, Japan, and Hawaii, and, indeed, in most other tropical and subtropical countries in which it has been searched for. Its ova are very frequently met with in the stools of natives of warm countries visiting England. According to Cobbold, it is not endemic in this country, but recent observations by Drs. Haldane, Boycott, and others shew that this immunity no longer obtains. It is frequently met with in the warmer regions of Europe and of North America, more especially in damp mines where the temperature is high and the sanitation defective. Englishmen returning from the tropics are sometimes affected.

The normal habitat of *A. duodenale* is the small intestine of man, particularly the jejunum; less often the duodenum, rarely the ileum or lower reaches of the alimentary canal; occasionally it has been found in the stomach. In these situations it attaches itself by means of its powerful buccal armature to the mucous membrane, large prolongations of which it sucks down into its oesophagus. This portion of the mucous membrane is destroyed. Some of the worms, and they may be free or

<sup>1</sup> Known by the American helminthologists as *Uncinaria duodenalis* Dubini 1843.

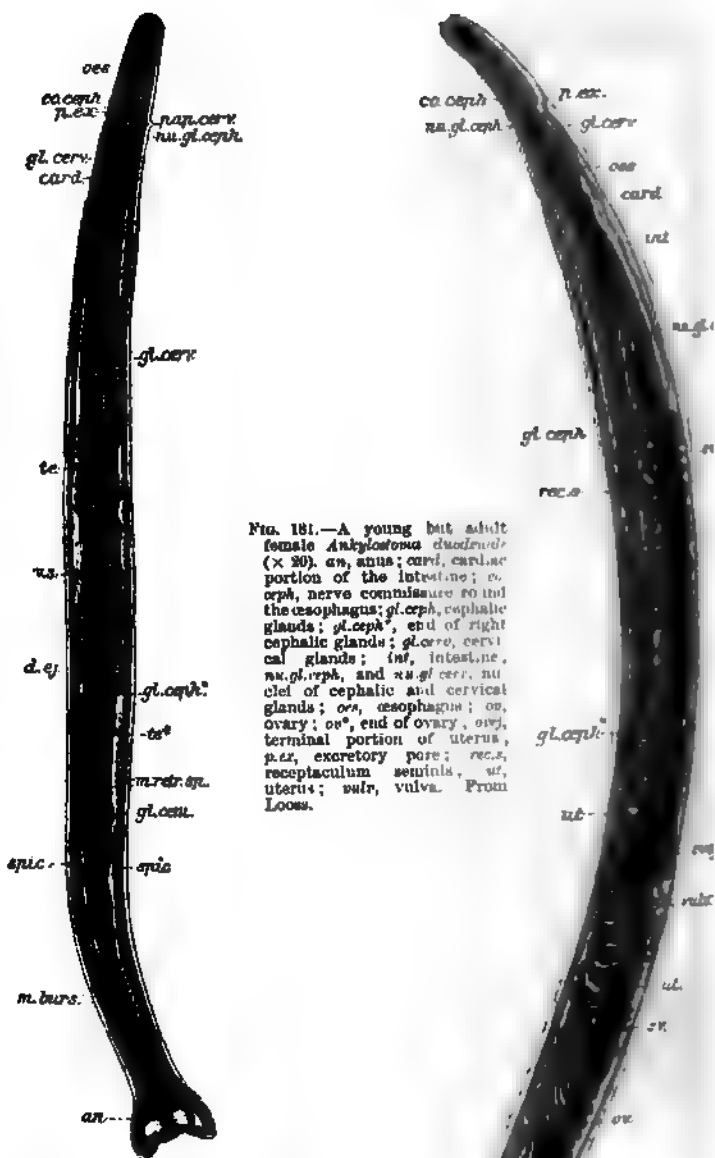


FIG. 181.—A young but adult female *Ancylostoma duodenale* ( $\times 20$ ). *an*, anus; *card*, cardiac portion of the intestine; *cc*, *ceph*, nerve commissure round the oesophagus; *de*, ejaculatory duct; *gl*, *rem*, remnant glands; *gl*, *cerv*, cervical glands; *gl*, *ceph*, end of cephalic glands; *gl*, *cerv*, cervical glands; *int*, intestine; *nu*, *gl*, *ceph*, and *nu*, *gl*, *cerv*, nuclei of cephalic and cervical glands; *oes*, oesophagus; *ov*, ovary; *ov*, end of ovary; *ov*, *ter*, terminal portion of uterus; *p*, *ex*, excretory pore; *rec*, *s*, receptaculum seminis; *ut*, uterus; *vul*, vulva. From Looss.

FIG. 180.—Adult male *Ancylostoma duodenale* ( $\times 20$ ). *an*, anus; *card*, cardiac portion of intestine; *cc*, *ceph*, nerve commissure round the oesophagus; *de*, ejaculatory duct; *gl*, *rem*, remnant glands; *gl*, *cerv*, cervical glands; *gl*, *ceph*, end of cephalic glands; *m*, *burs*, muscles of the bursa; *m*, *retr*, *sp*, retractor muscles of the spicule; *nu*, *gl*, *ceph*, nuclei of the cephalic glands; *oes*, oesophagus; *pap*, *cerv*, cervical papilla; *p*, *ex*, excretory pore; *spic*, spicule; *te*, testis; *te*, end of the testis; *v*, *s*, vesicula seminalis. From Looss.

tain fresh blood in their alimentary canal, others do not. Looss, if blood be present the corpuscles are undigested, the of the parasite cells comprising a layer of the It is supposed as hold from the abandoned blood for a e. The two glands, which e base of the s, discharge, it jected, some substance into the host.

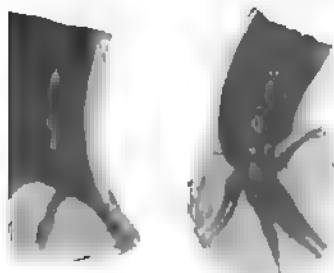


FIG. 182.—Head of *Ankylostomum duodenale* ( $\times 100$ ), looking into the mouth. *dent.l.*, the internal teeth, near the bottom of the oral capsule; *or. cap.*, entrance to the oesophagus; *pap.d.*, *pap.l.*, *pap.v.*, dorsal, lateral, and ventral head papillae. From Looss.

le and female  
ia — present  
n the propor-  
of the former  
the latter—do

much in size as do many of the other nematodes. The are from 8 to 10 mm. in length by 0.4 to 0.5 mm. in breadth;

12 to 18 mm. in length by 1 mm. in breadth. Both indrical in form; white when they are alive, grey when dead, rown when full of blood. In both sexes the posterior end is t part, whence the body tapers forward to a narrow neck, in the bulging and distinct mouth capsule. The margin arkable organ is furnished with four strong, claw-like hooks,



*a* *b*  
caudal bursa. *a* of the male of *Ankylostomum americanum*. Seen from the left. *b*. From Looss.

id delicate spicules project from the cloaca at the bottom of From the relative positions of the sexual openings the worms on look like the Greek "γ."

—PT. II

3 M

The female *Ankylostoma* produces a prodigious and never-ending stream of eggs which passes out in the feces of the host. These eggs (0.054 to 0.061 mm. by 0.034 to 0.038 mm.) have a regular oval form, with a dentate, smooth, and beautifully transparent shell, through which the greyish and distinctly segmented yolk can be readily seen. While in the body of the host development does not advance further, but on leaving it development proceeds, in suitable circumstances, so rapidly that in one to two days a rhabditiform embryo (0.2 mm. by 0.014 mm.) is born. This minute organism is very active, voraciously devouring what organic matter

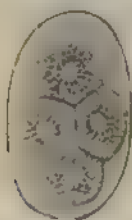


FIG. 184. Egg of *Ankylostoma duodenale* (• about 400). Colorless. From Looss.

it can find, and for a week it grows rapidly (to 0.56 mm. by 0.024 mm.). During this time it moults twice. After the second moulting it passes into a sort of larval state, during which it no longer eats and growth is suspended. In this condition it may live for weeks or months, moving about more or less languidly in muddy water, in mud, or in damp earth. Should chance so determine, the larva is finally transferred to the human alimentary canal either, as Looss has shewn, by boring through the skin, or possibly, but this is unlikely, by being carried to the alimentary canal in muddy drinking water, or in the mud or dirt adhering to the hands or dishes of the agriculturist, the brick-maker, or other operative engaged in handling the soil, or, it may be, in earth deliberately eaten by the geophagist. When the minute *Ankylostoma* larvæ, which have hatched out in the soil, come in contact with the skin of man, they immediately begin to bore through the epidermis, many of them passing along the hair-follicles. If in great numbers they cause a marked inflammation of the skin, and such nematode larvæ may in many cases be responsible for the dermatitis variously known as "cooley itch," "sore feet," "ground itch," etc., in tropical countries, and "bunches" in Cornish mines. Having reached the cutis they make their way into the lymph capillaries or later into the superficial veins. Thus they reach the venous system either directly or through the thoracic duct, and by this route are conveyed to the lungs. They then traverse the soft pulmonary tissues and emerge into the air-vesicles and bronchial tubules. Here they undergo their third ecdysis, and then wriggling up the mucous secretion in the bronchi and trachea, turn back at the glottis and pass down the oesophagus into the stomach. Arrived in its final host, after moulting again at the end of six weeks (Leichtenstern), they acquired sexual maturity and the permanent adult form. The duration of the life of *A. duodenale* in the intestine has not been determined; some state it in months, others in years. Senftenberg

Col. Giles holds that *A. duodenale* may become sexually mature outside the body and in the free state; in other words, that it is heterogonic. His observations have recently been confirmed in part by Dr. Sandwith, although doubt has been thrown on their relevancy by Sars and Macdonald.

v. *Necator americanus* Stiles 1903.—(Synonym: *Uncinaria americana* Stiles.)—The American hook-worm or tunnel-worm differs from the *Ankylostoma* in the absence of the four oral teeth. It is slightly shorter and clearly thinner than the *A. duodenale*, the male being 7 to 10 mm., the female 9 to 11 mm. in length. The head bends round towards the dorsal surface; the oral hollow is small, without any teeth on its free edge, but in place of them are two plates with cutting edges. Deep within the capsules are the ventral teeth, just as in *A. duodenale*. The lateral wings of the copulatory bursa in the male are prolonged so that the bursa seems two-lobed. The eggs closely resemble those of the European hook-worm, but are a little bigger (0.064 to 0.072 by 0.036 mm.), and they are slightly more pointed at the poles.

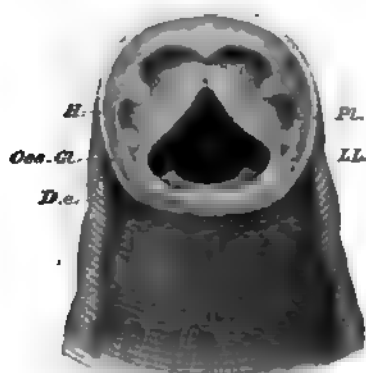


FIG. 185.—Head and mouth of *Necator americanus*, seen from behind ( $\times 330$ ). *D.e.*, dorsal free edge of the mouth; *H.*, skin of the head covering *Pl.*; *Oes. Gl.*, opening of the dorsal esophageal glands; *Pl.*, cutting plates inside the mouth; *LL.*, chitinous lamellae. From Looss.



FIG. 186.—Egg of *Necator americanus* ( $\times$  about 400). Colourless. From Looss.

The presence of this worm in the alimentary canal of the "poor white" or "mean white trash" of the Southern States has been recently the subject of much research. We are still in ignorance of many of the details of the development of *N. americanus*, but it probably differs little from that of *A. duodenale*; the clinical symptoms it gives rise to closely resemble those caused by the latter.

This species has recently been shewn to occur in the intestines of the six pygmies (Looss) belonging to the Mhute, who were recently exhibited in London. Thus, we must add as well as both Americas the central part of Africa as the home of this parasite. The pygmies also harboured an *Ascaris* sp., *Schistosomum hematobium*, *Trichocephalus trichiurus*, and *Oxyuris vermicularis*. *Necator americanus* also occurs, according to Dr. J. W. W. Stephens, in Madras, Assam, and Burma.

**Ankylostomiasis.**<sup>1</sup>—Considering the insignificant size of these

<sup>1</sup> The Americans have called this disease Uncinariasis.

parasites, it is unlikely, so long as the numbers are small, that serious inconvenience should result from their presence in the intestine. But when these numbers mount up to hundreds or thousands, as is often the case, as a result of the constant drain of blood they keep up for months or years, the dyspepsia and malnutrition entailed by their presence, the wounds they inflict on the mucous membrane, and it may be the hæmolytic toxin they secrete, a grave cachexia—the state known as ankylostomiasis—is produced and not infrequently leads to a fatal issue.

The recognition of this form of helminthiasis as an important pathological condition is of comparatively recent date. Griesinger was the first to point out that the form of anaemia known as Egyptian chlorosis is of this nature, and, later, other observers shewed that a similar anaemia was common among negroes in America. Public attention, however, was not forcibly directed to the subject until 1880, when the occurrence of the notorious epidemic of anaemia among the workmen engaged in making the St. Gothard tunnel was shewn to be of this nature. It was subsequently discovered that similar anæmic conditions originating from the same cause were not uncommon among the workmen employed at certain European mines, and recently it has been proved that the parasite and the cachexia to which it gives rise are exceedingly common throughout the tropical and subtropical regions. The parasite has lately been very common in the Westphalian coal fields, and has recently been imported into the tin mines of Cornwall.

As with many discoveries on their first being made known, the importance of the *Ankylostoma* was exaggerated, not a few diseases—beriberi for example—being attributed to it with which it is in no way concerned. Nevertheless, although many of the diseases for which it has been blamed have nothing to do with the *Ankylostoma*, it cannot be doubted that this parasite in many instances, and in the aggregate, well deserves the evil reputation it has acquired.

The exact conditions under which *Ankylostoma duodenale* becomes gravely pathogenetic are perhaps not yet thoroughly understood, for we meet with all the symptoms of pronounced ankylostomiasis in patients whose intestines contain comparatively few ankylostomes, whereas these parasites may be present, even in vast numbers, in persons who are, notwithstanding, to all appearance healthy and robust. In determining the establishment of this cachexia much must depend, therefore upon individual idiosyncrasy in respect of digestive power, and on the tolerance of blood depletion and of intestinal irritation, also on the individual physiological margin, on the conditions of physical work, and on the quantity and quality of aliment obtainable. It can be readily understood that a vigorous, healthy European, well nourished on flesh, eggs, and milk-like concentrated and easily digested foods, will stand a larger invasion of *Ankylostoma* than the feeble, limp, labouring Indian. The latter to obtain sufficient nutriment from his coarse dietary of sweet potatoes, rice, vegetables, and other bulky and unnutritious foods, has so to stuff his stomach three or four times a day that dilatation of that organ, and the



various catarrhal and dyspeptic conditions thus entailed, must necessarily ensue; doubtless these concomitants have a large share in the production of the pathological picture in which the *Ankylostoma* is only one, though perhaps the leading feature.

Then, again, in many tropical countries a considerable proportion of the population lives in a chronic state of semi-starvation hard for us to realise. Under such conditions the daily loss of blood which a few hundred ankylostomes entail is a serious matter, and may be all that is required to turn the scale and start the vicious circle of famine degeneration.

*Symptoms.*—The essential symptoms of ankylostomiasis are those of a progressive anæmia generally associated with symptoms of intestinal catarrh leading in time, if not checked, to fatty degeneration of the heart and other organs, and ultimately to serous effusions and death.

Pain in the epigastrium radiating towards the umbilicus, increased by pressure, but generally relieved by food, is one of the earliest signs of invasion by *Ankylostoma*. This pain may be accompanied by dyspeptic troubles, colicky symptoms, and borborygmi. The appetite is very often ravenous, although the digestive powers may be feeble; occasionally there is anorexia. Perverted appetite—pica or geophagy, as it is sometimes called—is a common occurrence in this as in other forms of intestinal helminthiasis, and is especially dangerous in ankylostomiasis, as in this malady its indulgence may tend to increase the infection. The bowels, generally constipated at first, may in the advanced disease be loose and irregular. Sometimes, though rarely, the stools have a reddish-brown tinge from sanguineous admixture, and pieces of blood-tinged mucus may be passed; but pure blood is rarely seen, for, though escaping, perhaps in considerable quantity, from the wounds made by the parasites in the upper part of the intestine, it is so mixed with the chyme, and so altered by the intestinal juices, that it is not recognisable in the stools. Temperature is usually subnormal; at times there may be transient flashes of fever.

As the disease advances signs of anæmia set in—such as pallor of mucous surfaces and complexion, breathlessness, lassitude, palpitations, hæmic bruits, tinnitus, dimness of vision, vertigo, depression and apathy, irritability of the circulation, attacks of syncope, cedema of the feet, and the usual train of symptoms attending recurring and prolonged hæmorrhage. Retinal hæmorrhages have also been observed.

Secondary dyspeptic conditions, such as gastralgia, vomiting, hæmatemesis, dilatation and ulceration of the stomach, often complicate and aggravate the more pronounced cases. Yet, strange to say, with all this anæmia and the secondary dyspeptic conditions, provided the feeding be good and sufficient, the patient remains fat and plump; the intense pallor and cedema being the only signs which force themselves on the attention.

Progress is sometimes very rapid; in a few weeks the patient may be brought to a dangerous state of anæmia, and even death may occur from

syncope or serous effusions. The vast majority of cases, however, have a more chronic course, extending over years; in these, if death result, it is often due to some intercurrent disease.

In children, not only does the *Ankylostoma* produce anæmia, but it stunts the growth and delays the occurrence of puberty. When such children grow up—particularly if malarial cachexia be combined with ankylostomiasis—they remain childish in appearance, puny in size, sexually immature, and with characteristic high-pitched treble voices.

Drs. Boycott and Haldane have shewn that, as in chlorosis, the total volume of the blood is much increased, whilst the total oxygen-capacity is slightly diminished. The average increase in volume in their cases was 94 per cent, the average decrease in oxygen-capacity 11 per cent. The number of red blood-corpuscles per c.mm. is usually decreased: in anæmic cases they may fall as low as 800,000; Dr. Sandwith gives 1,290,000 as an average of 173 anæmic cases. The characteristics of the so-called Egyptian chlorosis set up by this parasite are—(1) severe anæmia; (2) very low hæmoglobin averages; (3) very low colour-index; (4) the frequent presence of normoblasts and in some cases of megaloblasts, but never a majority of megaloblasts; (5) the frequent presence of poikilocytes and of cells shewing polychromatophilic staining.

The total number of leucocytes per c.mm. are in cases of recent infection usually increased, and the amount of this increase is quite independent of the other symptoms exhibited. Drs. Boycott and Haldane record counts up to 56,000 in cases of recent infection, which were not associated with any severe symptoms. The main feature, however, of the blood in these cases is the presence of an eosinophilia, with both an absolute and a relative increase of the eosinophil coarsely-granular blood leucocytes. This feature is so characteristic of infections with this nematode that Dr. Boycott recommends a differential count of the blood leucocytes as the first line of evidence in diagnosing the disease, when a large body of men have to be subjected to examination. The degree of eosinophilia varies with the total leucocyte count, and is most constant and best marked in those persons who are not suffering from anæmia; that is, in those persons who shew nothing which would suggest that they harbour the worm. Ninety-four per cent of the 148 cases of *Ankylostoma* infection examined by these authors shewed an eosinophilia of more than 8 per cent with an average of 18 per cent. Their highest figures are 66 per cent in two cases of recent infection, with total leucocyte counts of 56,000 and 44,000 per c.mm. respectively.

As the disease becomes more chronic the percentage of eosinophil cells tends to fall, but in such cases, after treatment, a rise in the number of eosinophils is to be expected, and at any time such a rise is of good prognostic import. Ashford and other American writers, working on cases of patients infected with *Necator americanus*, have confirmed these general results on persons harbouring that parasite.

*Diagnosis.*—The secret of the diagnosis of ankylostomiasis, like that of

so many other diseases, is to suspect its presence. Microscopic examination of the fæces justifies or dismisses this suspicion at once. If ova are found, some idea of the extent of the infection may be got from an enumeration of the eggs in a given quantity of fæces. According to Grassi and Parona, 150 to 180 eggs per centigramme of fæces indicate approximately an infection of 1000 worms, male and female together. Sometimes it happens that although the *Ankylostoma* has disappeared the subsequent anæmia and degenerations progress, even to a mortal issue, the fatal pathological circle of famine changes having become established before the worms had been got rid of. In these cases ova are, of course, absent from the stools, and a diagnosis can only be guessed at from a consideration of the history and other circumstances. On the other hand, although a certain number of ova may be met with in the stools of some cases of anæmia, the diagnosis of ankylostomiasis must not be jumped at without a careful consideration of the entire circumstances of the case, and a careful exclusion of such causes of anæmia as malarial disease, Bright's disease, cancer, tuberculous disease, idiopathic pernicious anæmia, leukæmia, and so forth. It should always be borne in mind that the majority of the natives in many warm countries harbour *Ankylostoma* and *Trichocephalus* besides the more readily recognised *Ascaris lumbricoides*; and that, therefore, the presence of any or all of these parasites may be expected in many diseases for which they are not in the slightest degree responsible.

In every case of tropical anæmia the possibility of ankylostomiasis should be entertained, more especially if on examination of the blood a pronounced eosinophilia be discovered, or if a history of small boils or papular eruption, especially about the hands or feet, has been elicited. Eosinophilia occurs in most verminous infections, but when concurrent with pronounced anæmia it is particularly significant of ankylostomiasis, and plainly calls for a microscopical examination of the stools for the ova of this parasite.

The pathological anatomy is that of extreme anæmia, plus the local lesions in the small intestines produced by the ankylostomes. Besides the extreme pallor and bloodlessness of all the tissues, there is general œdema, and often also effusion into the serous cavities. Many of the viscera shew signs of fatty degeneration, particularly the heart, which is pale, yellowish, flabby, and dilated. Some pathologists have described an excess of iron in the liver, pointing to a hæmolytic as well as a simple hæmorrhagic origin for the anæmia; such a hæmolysis they attribute to the absorption by the intestine of some product of the parasite. Other observers deny any excess of iron in the liver, and, consequently, the toxic absorption referred to. If careful search be made soon after death in the small intestine the *Ankylostoma* may be found still attached by the mouth to the mucous membrane; if the post-mortem has been delayed the parasites will be found loose in the mucus. Scattered about the intestine, in and under the mucous layer, and shewing through the serous and muscular coats of the pallid bowel, a number of small

ecchymoses are to be seen. If the centres of these be carefully scrutinised the minute wound inflicted by the ankylostome can be detected. In rare instances parasites have been found, singly or in pairs, in a blood-filled cavity the size of a filbert underneath the mucous membrane—a minute aperture, the hole by which the worms had entered, opening into it. The sites of old hæmorrhages are indicated by punctiform pigmentation. At times there may be thickening and even swelling of the mucosa, and other signs of old and recent catarrh. The mucous membrane of that part of the bowel where the parasites are located is usually streaked with blood, rarely (although such cases are on record) is the bowel found filled with a more extensive hæmorrhage.

*Treatment.* Until the introduction of thymol by Bozzolo in 1880 the extract of male fern, in heroic and sometimes toxic doses, was the only efficient anthelmintic in ankylostomiasis. In Brazil the juice of the *Ficus doliocarpa* enjoyed a certain reputation. Both of these remedies were superseded by thymol, which had the further advantage of being effective against a variety of intestinal parasites, such as tapeworm, *Enterobius vermiciformis*, *Haemodiscus hominis*, and possibly others. Beta naphthol is also used, and quite recently oil of eucalyptus has been advocated. It is very effective, and, being less toxic and much more pleasant to take, is likely to supersede filix mas, thymol, and beta naphthol.

To be effective thymol must be given in full doses, 15 to 40 grains, repeated three or four times at intervals of one and a half to two hours. If the bowels do not act spontaneously within twelve hours of the last dose a purgative should be given. It is well to clear out the bowels the day before the administration of the thymol, and to place the patient for the time being on liquid diet. It is best administered in capsules or tablets. In hospital or dispensary practice in the endemic districts considerations of expense suggest that it had better be given in suspension, care being taken that it is finely triturated before mixing. A draught may be served out from a stock-bottle so prepared. Although thymol is very insoluble in water there is some danger of irritating its use and arising from its absorption in poisonous amount. One precaution must be taken against such a mishap. Thorelli of Ceylon, as well as others with extensive experience in the use of the drug, state this most emphatically, and refer to several deaths from convulsions after full doses. Thymol is very soluble in alcohol, ether, turpentine, chloroform, oil, certain alkali solutions, and in glycerin. Therefore, during treatment, and while the drug is still in the alimentary canal, these solvents must be carefully withheld. These dangers and precautions are, as a rule, not sufficiently recognised by practitioners, nor insisted on by authors. Signs of thymol poisoning, such as delirium, vertigo, and dark brown urine, must be regarded as indications that the use of the drug should be suspended for a time.

Eight days after a course of thymol or beta naphthol, which may be prescribed in the same way, the stools should again be examined microscopically. If ova are found to be still present the drug should be

repeated. A certain proportion of the ankylostomes resist its action, hence the necessity for readministration.

Eucalyptus oil should be given in combination with chloroform and castor oil. The method recommended is to prescribe min. xxx, chloroform min. xlv., castor oil ̄x. Half of this is given in the morning, fasting, the other half thirty minutes later. The drugging may be repeated every other day, or as long as eggs are found in the stool. After the expulsion of the parasites has been secured the anæmia should be treated by iron, dieting, and on ordinary principles.

*Prophylaxis*.—In all countries in which ankylostomiasis is endemic great care should be taken to secure a pure water-supply. Where this is impracticable all drinking-water should be boiled or filtered. Agriculturists, brick-makers, miners, and all those whose hands or feet are apt to be soiled with earth or clay, must wash most carefully before eating, and on returning from work; field-workers should be encouraged to wear shoes and putties. In villages and plantations those responsible for the health of the natives should prevent contamination of the water-supply and of the ground by the indiscriminate casting of night-soil about; and also insist on the systematic use of privy trenches, or other suitable contrivance, in which the fæces may be disinfected or effectually and permanently covered up.

Coolies should be regularly inspected, and anæmic individuals should be examined for ankylostomes and treated if necessary. The workers in infected mines should be similarly inspected, and the mines kept as dry, cool, and sanitary as possible.

vi. *Triodontophorus deminutus* Railliet and Henry 1905. A new species allied to the Strongylidæ has recently been described by Railliet and Henry. The worms are cylindrical, pointed at each end, and striated transversely. The buccal capsule contains three teeth. The male is 9.5 mm. long. Its genital bursa is broader than long. The female is 11.7 mm. long. The eggs are 0.06 by 0.04. The parasites came from a negro's intestine at Mayotte. The genus *Triodontophorus* usually inhabits the large intestine of the Equidæ.

vii. *Æsophagostomum brumpti* Railliet and Henry 1905. The same observers have also described this new species, taken from tumours in the large intestine of an African negro. Only immature females were found. Their length was 8.5-10 mm. There are six cephalic papillæ and an oral circle of twelve spines. The genus is found in several mammals, including monkeys and apes. The young forms usually occur in nodules in the intestinal wall.

### Family III.—Trichotrachelidæ

So called from the long thin "neck," at the end of which is placed a simple, punctiform mouth. The œsophagus in all the species constituting this family is also very long and moniliform. The "body," which contains the reproductive organs, is thicker. The spiculum is single or

absent. There is only one ovary; the female reproductive pore is at the junction of "neck" and "body."

i. *Trichocephalus trichiurus* (L.) 1771. — (Synonyms: *Ascaris trichiura* L. 1771; *Trichocephalus hominis* Schrank 1788; *Trichocephalus dispar* Rud. 1801.)—This parasite, known as the whipworm, whose principal habitat is the cæcum, measures in length, in the case of the male worm, 40 to 45 mm., in the case of the female worm 45 to 50 mm. It looks as if made up of two portions—(first) the long filiform neck, which somewhat abruptly expands into (second) the thick and relatively short body: it reminds one in shape of a certain pattern of whip—hence its name in the vernacular.

In the male the posterior part, or body, is disposed in a spiral of one or two turns; it ends abruptly. The cloaca, from which the single spicule (2.5 mm. long) and its sheath usually protrude, is terminal. In the female the body is nearly straight and tapers gradually to the pointed end, the anus—a transverse slit—being subterminal. The vagina opens at the root of the neck. The cuticle in both sexes is transversely striated, and is further marked by a longitudinal band of minute papillæ extending from head to tail along the ventral surface. Uterus and testis are single, and fill the thick posterior part of the worm. The long neck is occupied by the œsophagus only.

The ova, with which the uterus and capacious vagina are crowded, measure 0.05 to 0.054 mm. by 0.023 mm. They are oval, brown, thick shelled, and are readily distinguished from all other intestinal ova by the clear pale bodies which mark both poles of the oval. At these points the shell is deficient, the holes so formed being

plugged by a sort of tampon of a clear homogeneous material (Fig. 188).

Like the ovum of *A. lumbricoides*, that of *T. trichiurus* contains no differentiated embryo on first leaving the parent worm: it has to pass a long time—many months, sometimes as many as eighteen—in water before the embryo is developed and ready for direct transference to the human stomach. The ova are possessed of great resisting powers, and may be frozen or desiccated without permanent injury to their vitality. The embryo requires no intermediate host, but reaches the stomach in water or in food while still *in ovo*; here the shell is dissolved and the embryo liberated. In four or five weeks—as has been proved by direct experiment—the young parasites arrive at sexual maturity.

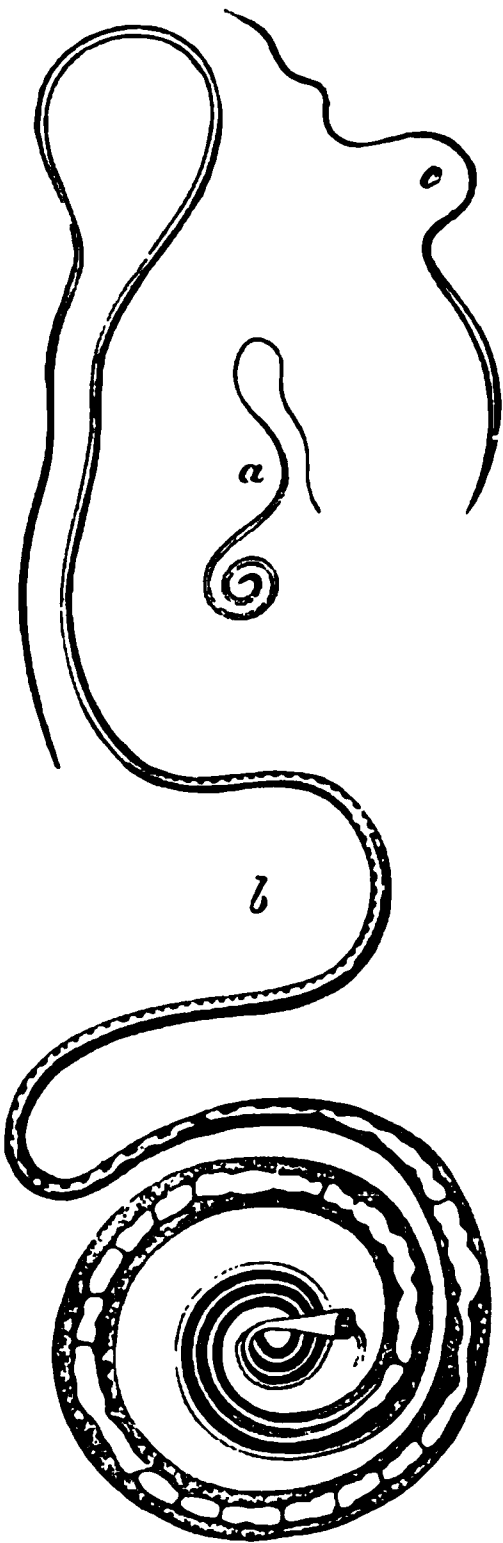


FIG. 187.—*Trichocephalus trichiurus*. a, male (nat. size); b, male (enlarged); c, female (nat. size). After Blanchard.



Although the usual situation of the *Trichocephalus* is the cæcum, it is found at times in the other sections of the alimentary canal, even in the stomach. The latter rarely occurs; but it is very often found at the lower end of the ileum, in the vermiform appendix, and in the ascending colon. Usually it lies loose in the gut; occasionally, however, specimens are encountered which cannot be readily displaced, and which, according to Leuckart, have fixed themselves to the mucous membrane by transfixing a fold of it with their long necks as with a pin, the fine end emerging on the surface of the mucosa some distance from the spot to which the body seems to be attached. Other observers deny that these worms so fix themselves. Metchnikoff has, however, drawn attention to the fact that the long neck of this worm sometimes pierces the wall of the cæcum or appendix, and by letting out the intestinal contents with their bacteria, peritonitis and appendicitis are set up. Besides man, certain species of ape and lemur harbour this parasite.



FIG. 188. — Egg of *Trichocephalus trichiurus* (X about 400). Colourless. From Looss.

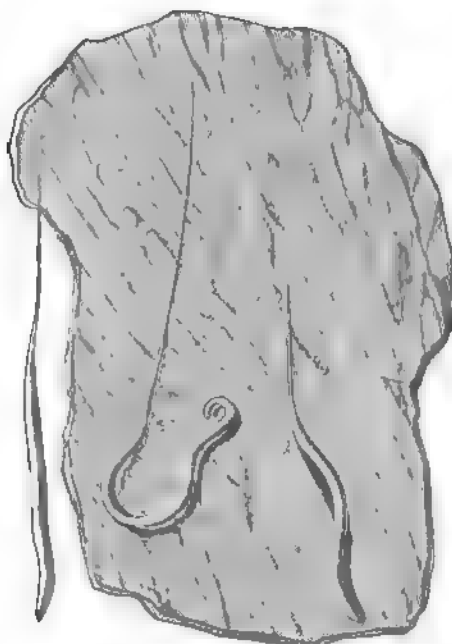


FIG. 189. — *Trichocephalus trichiurus* Rnd., attached to part of the human colon (X 2).

In *T. trichiurus* the sexes are about equal in numbers; if anything, the males are the more numerous. It is a rare thing to find more than a dozen or two specimens in one body, but every now and then cases of a

high degree of infection are met with in which the caecum contains hundreds and even thousands of these parasites.

In its geographical distribution the *Trichocephalus* is cosmopolitan. Speaking generally, it may be said to be more common in the inhabitants of warm than in those of cold climates. There are many local circumstances, particularly the character of the water supply, which have an important influence in determining the proportion of inhabitants affected in any given place. In Paris, for example, Davaine believed that one half the population were affected. In Dresden, of 1939 individuals in whom the *Trichocephalus* was sought for it was found in only 2.5 per cent; in Erlangen, of 1755 individuals it was found in 11.11 per cent; in Kiel, of 611 individuals in 30.6 per cent. It is very common in the Malay Archipelago, as elsewhere in the tropics; thus, in Sumatra, Erni found it 24 times in 30 autopsies.

The *Trichocephalus*, so far as is known, has very little pathological significance, except when it perforates the intestine. A few cases are recorded in which nervous symptoms were found in association with a high degree of infection. But there is no adequate ground for supposing, as some have asserted, that it is in any way responsible for such diseases as typhoid fever or beriberi.

Several cases of anaemia (some fatal) are reported as caused by the presence of this parasite—the blood shewing a fall in the number of red cells, marked poikilocytosis, and the appearance of nucleated red corpuscles mainly of the normoblastic type. In some few cases it seems to have set up eosinophilia, but this appears not to be the rule.

*Treatment*—Although these worms are often expelled accidentally by the male fern, santonin, or thymol administered for other kinds of intestinal worms, these drugs are by no means to be relied on as specific against *Trichocephalus*. No good anthelmintic is known for this parasite.

*Prophylaxis* should consist in securing a pure water supply, or in boiling or filtering drinking water when it is not absolutely above suspicion.

11 *Trichinella spiralis* (Owen) 1835 —(Synonym *Trichina spiralis* Owen 1835) Although the muscle, encysted, or larval form of *T. spiralis* (Fig. 196) had been previously seen by one or two observers, to Sir James Paget belongs the merit of being the first to recognise the true nature of these bodies. His discovery was confirmed by Owen, who, in 1835, gave the parasite the name of *Trichina spiralis*. But as the name *Trichina* proved to be preoccupied, Railliet has called it *Trichinella*. Since that time much attention has been paid to the subject, principally by German observers; so that at the present day the history of the parasite and the important pathological states to which it gives rise are fairly well understood.

If the voluntary muscles of a man or other animal affected with trichinellosis be examined with a lens, and the examination be made any time after the fifth or sixth week from the date of infection, an innumerable multitude of minute cysts, each including a tiny coiled-up worm, can

be seen dotted about the tissue, and lying between and slightly separating the fibres. If a fragment of the affected muscles be excised, laid on a glass slip, teased out, lightly compressed beneath a cover-glass, and then examined with a magnifying power of some forty or sixty diameters, as the slide is slightly warmed, or a solution of potash added to it, the little worm is seen to move. It is therefore alive. This is the encysted or larval form of *Tr. spiralis* (Fig. 190).

The cyst, in which the *Trichinella* lies surrounded by a clear albuminous fluid, is oval or rather, lemon-shaped in form, having two more or less pronounced diverticula at the poles. Its long diameter, which corresponds in direction with the muscular fibres, may be set down on an average at 0.4 mm., and its short at 0.25 mm.

The capsule of the cyst is chitinous in character and lamellated; it varies a good deal in thickness according to the part of the cyst examined and to its age, being always thickest at the poles and in the oldest cysts, and least dense and most transparent in young cysts and about the equator. Some cysts are more globular than others. Most of them contain only one *Trichinella*, but cysts containing two or more, even up to six or seven, are frequently encountered.

In cold and dead muscle the included *Trichinellæ* are quite passive, and lie rolled up in a close spiral of four or five turns. In warm and fresh muscle the spiral is more open, and more in contact with the cyst-wall, over which the head end of the worm is seen to move slowly. The worm itself is cylindrical, tapered off anteriorly to relatively small dimensions, thicker posteriorly, where it is abruptly rounded off. It measures from 0.8 mm. to 1 mm. in length by 0.04 in width. The mouth opens at the fine end, the anus at the thick end, an alimentary canal of the type characteristic of the Trichotrachelidæ running between these two points. In addition to the straight alimentary canal the rudiment of the sexual organs can be made out as a thick tube occupying the greater part of the ventral portion of the posterior half of the body; development in this respect, though not complete in the encysted worm, is well advanced, the sexes being already distinguishable.

If a piece of raw flesh containing these encysted *Trichinellæ* be eaten by man or by certain of the lower animals, the cysts are dissolved by the gastric juices and the parasites liberated; they then quickly pass into the small intestine, where the sexual organs rapidly complete their

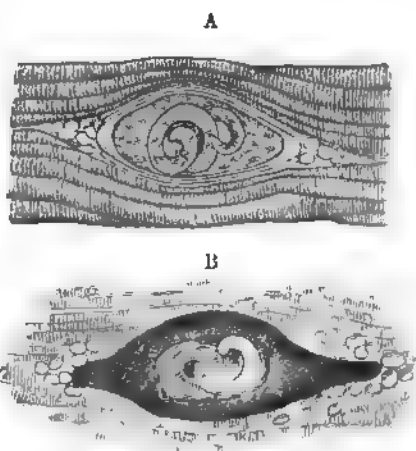


FIG. 190. *Trichinella* capsule with connective-tissue covering. A, alive; B, capsule calcified.

development. At the end of about two and a half days impregnation is effected.

At this stage the worms have grown slightly—the male to 1.4-1.6 mm., the female to 1.5-1.8 mm. Both sexes retain their cylindro-conical shape, but the male is now seen to be provided at the posterior end with two appendages resembling the jaws of a pair of pincers. These organs form a sort of copulatory bursa, their function being to fix the female *in coitu*. The male has no spicule, but the cloaca can be evaginated, thus forming a penis. Between the caudal appendages lies the cloaca, and behind the cloaca two small papillæ. In the female the single ovarian tube runs forward to terminate in the vulva on the ventral surface about the junction of the anterior with the second fifth of the body. In both sexes the oral end is very finely pointed, carrying at its tip the punctiform mouth.

When copulation takes place the female has not attained her full size: she is then but little larger than the male worm. Impregnation effected, however, the male worm dies, and the female grows rapidly to two or three times (3-4 mm. by 0.06 mm.) her original size. Growth takes place principally in the posterior part of the body, and is apparently a consequence of the rapid development of the ovarian contents. The *Trichinella* is ovo-viviparous. The upper part of the oviduct is filled with segmenting ova; lower down the embryo becomes apparent, enclosed in its vitelline membrane; lower still this membrane disappears, and the embryo is free. The first of the young *Trichinellæ* are born about the sixth or seventh day from the date of infection. The parent worm continues to pour forth her young in a continuous but, after a time, diminishing stream during the following five or six weeks, when, after having given birth to a swarm of many thousands, she dies and is voided.

The young *Trichinellæ*, which are minute, lancet-shaped organisms with a thick, rounded anterior which gradually tapers to a fine tail, measure about 0.1 mm. by 0.006 mm. There are two views as to how the larvæ make their way into the muscular tissue. The first is that soon after birth they penetrate and traverse the walls of the intestine, cross the peritoneal cavity, and, travelling along the connective-tissue spaces, finally come to rest in voluntary muscle and in certain other tissues. The second, and at present more generally accepted, view is that the gravid female bores through the tissue of the intestine until she reaches a lymph-vessel. Here she discharges the embryos, which are carried by the stream of lymph all over the body, coming to rest mainly in the striated muscles. At the close of their migration they measure 0.12 mm. in length. During this journey, which, according to the distance travelled, may last a longer or shorter time up to ten days, the *Trichinellæ* increase slightly in size, and traces of an alimentary canal begin to appear. On arrival at its destination, the inside of a muscular fibre, they give rise by their movements and presence to a certain amount of irritation, leading to proliferation of the

connective-tissue cells in its immediate neighbourhood. In and probably from the exudation so produced, the capsule of the cyst, already described, is moulded, the moulding process possibly being effected by the rotatory movements of the worm now passing into its larval and passive state. Some helminthologists believe that the cyst-wall is formed, not in the way described, but very much as the cyst-wall of the trematode larvæ is formed, namely, from a secretion proper to the animal itself.

Step by step with the progress of encystment the parasite gradually ceases to move; it then coils itself up, and, increasing in size, assumes the larval characters already described. Eighteen days from the time of infection this process is complete; after that the young larva, on being transferred to the stomach of another animal, is capable of attaining sexual maturity.

In the encysted state the *Trichinella* retains its capacity for further development for many years—five, ten, even twenty years. Ultimately, however, the cyst undergoes fatty and calcareous changes, and the parasite it contains dies.

Such, briefly, is the life-history of the *Trichinella spiralis*. It is manifest that, cannibal countries excepted, man cannot possibly be the normal host of the parasite; nor, although the pig is the invariable medium of infection for man, can we



FIG. 191.—Mature *Trichinella spiralis* (magnified).  
A, female; B, male.

regard even the pig, which in a state of nature has few opportunities of indulging its carnivorous propensities, as the proper host. It is believed that *Trichinella spiralis* is normally and properly speaking a parasite of the rat; and that its occurrence in other animals is more or less of an accident depending on the artificial conditions of life imposed by civilisation. Rats are known to devour each other as well as the dead bodies of any other animals they may chance to come across; and it is believed that it is by this animal, and in this way that, in the natural order of things, the species *Trichinella spiralis* is kept in existence and transmitted. Systematic examination of the rats of different countries proves the extreme liability of this rodent to *Trichinella* infection, and tends to bear out this view. Thus, an investigation in Germany shewed that 8·3 per cent of the rats in certain places were trichinellised. A similar inquiry in the United States of America yielded still more remarkable results; for in some localities 10 per cent of the rats were affected, in other localities even 100 per cent. Impressed by these and similar facts, some naturalists have suggested that *Trichinella spiralis* was introduced into Europe from Asia by the grey rat, which first made its appearance in Germany in 1770.

It is further believed that the pig in the first instance is very often infected by eating dead and trichinellised rats which had died in or been thrown into its sty, or which it may have come across and devoured in the course of its grubblings. The liability of the pig to infection, however, is further and very much increased by the thoughtless way in which, too often, it is fed on kitchen slops, on scraps of offal, and on the washings and refuse of slaughter-houses, which may very well contain—particularly in large killing and packing establishments such as those in America—fragments of trichinellised swine's flesh. In this way the offal of a single trichinellised carcase may infect an entire herd; and one can readily conceive of circumstances, particularly in those large establishments in which swine are bred and fattened as well as slaughtered, whereby this systematic feeding on offal must inevitably lead not only to general trichinelliasis of the stock, but to an increasing and finally an extreme degree of this most dangerous form of parasitic disease.

Another point of practical importance is the circumstance, now thoroughly established, that the larval *Trichinella* encyst themselves, not only in the voluntary muscles, but also in the connective tissue of many other organs, notably in the panniculus adiposus and in the coats of the intestine. In this way it comes about that they are to be found in lard, in sausage skins, and in other food preparations, which might be looked upon as unimportant by-products of the pork factory. Of all the muscles of the body the diaphragm, and particularly its pillars, is most subject to trichinelliasis; next to it the intercostal muscles; the muscles of the neck, and the muscles of the eye; in the larger muscles the parasites are most numerous near the tendinous ends. Now it so happens that these parts form just the scraps which in economically conducted establishments are worked up into sausages and similar preparations: hence the



many accidents that have occurred from eating such things when imperfectly cooked. Next to those already enumerated, the muscles of the upper part of the trunk are most liable to infection; then those of the lower part of the trunk; of the muscles of the limbs, those nearest the trunk are most affected. It may be mentioned that the heart rarely contains *Trichinellæ*.

Another point of great practical importance is the remarkable resisting powers displayed by the *Trichinella* as against decomposition, high and low temperatures, desiccation, and the action of the chemical substances employed in pickling. *Trichinellæ* which had lain in putrid meat for over 100 days were still alive; and Fourment has shewn that the *Trichinellæ* in pork which had been steeped in pickle were still alive at the end of fifteen months, and were capable of infecting and killing mice in a very few days. Benecke also has shewn that the *Trichinellæ* in hams and sausages which had been in pickle for twelve days and then smoked were alive nine months afterwards. Neither are they killed by temperature as low as  $-20^{\circ}\text{C}$ . Leuckart exposed a ham during a whole night in winter, and also during three days when the temperature ranged from  $-22^{\circ}$  to  $-25^{\circ}\text{C}$ ., and yet the *Trichinellæ* it contained survived.

Still more remarkable and important is the tolerance by this parasite of high temperature. Perroncito asserts that on the stage of the microscope an exposure of a few minutes to a temperature of from  $48^{\circ}$  to  $50^{\circ}\text{C}$ . suffices to kill it. Other observers, however, maintain that in other and more ordinary circumstances the parasite will resist a temperature of  $60^{\circ}$ ,  $70^{\circ}$ , or even of  $80^{\circ}\text{C}$ . If this be so, it is evident that the *Trichinellæ* in the centre of a large joint of pork will not be killed by cooking as ordinarily conducted, and that the *Trichinellæ* in chops or cutlets apparently well cooked may still be alive. It has been shewn that after two hours' boiling the temperature at the centre of a large ham had only risen to  $33^{\circ}\text{C}$ .; after six hours to  $65^{\circ}\text{C}$ .; and that it was only after ten hours' hard boiling that  $85^{\circ}\text{C}$ . was reached. Hence, to be really effective against the *Trichinella*, the cooking of pork and ham must be much more prolonged and thorough than is customary. Little wonder, therefore, that several epidemics of trichinelliasis have been caused by swine's flesh cooked in the ordinary way. That of Posen, occurring in 1863, in which seven persons were attacked after eating food which had been cooked for an hour and a half, is an instance in point; the Workington epidemic in 1871, as narrated by Cobbold, is another instance. That this is the only epidemic recorded as occurring in Britain is in some measure attributable to the thorough way in which food is cooked in this country as compared with Germany; the same remark applies to France, Italy, and especially to China.

*Geographical Distribution.*—As rats and pigs are now found in all lands, *Trichinella spiralis* is one of the cosmopolitan parasites. It is more common, however, in some countries than in others, its degree of frequency being probably in great measure influenced by the habits of the human inhabitants in the matter of pig-keeping and pig-feeding. In

Great Britain it is rare; it is rare also in France and in Italy. It is common in America, Holland, Denmark, Sweden, and Germany. Thus, of 53,318 pieces of American pork or preparations of pork examined at Havre, France, 1087 pieces, or 2.03 per cent, were found to contain *Trichinellæ*; observations made in different parts of America variously state the proportion of trichinellised pigs at from 5 to 8 per cent. In Germany, at Rostock, one pig in 336 was trichinellised; in Brunswick one in every 5172; and in Prussia one in about every 2000. In India the *Trichinella* is said to occur frequently. In China (Amoy) the parasite was found twice in 219 carcasses.

**Trichinelliasis or Trichinosis.**—For many years subsequent to its discovery *Trichinella spiralis* was looked upon as an innocuous parasite—a curiosity, but in other respects of no interest to the pathologist. In 1860 a series of brilliant discoveries by Zenker, Virchow, Leuckart, and others, placed the matter in a very different light, and conclusively proved that the *Trichinella* and trichinellised pork were responsible for many peculiarly localised and very deadly epidemics, the nature of which had not hitherto been understood.

In the year referred to a young girl died in hospital at Dresden, it was supposed of enteric fever. A marked feature in her case had been severe pains in the muscles. At the post-mortem examination no ulceration of Peyer's patches was discovered. When Zenker came to examine the muscles which had been the seat of so much pain, he was astonished to find that they were stuffed with *Trichinellæ*; and when, in consequence of this discovery, he directed his attention to the contents of the alimentary canal, he had no difficulty in finding there numbers of adult parent worms. The girl had evidently died, not of enteric fever as was supposed, but of trichinelliasis. Pursuing the subject Zenker traced the girl's infection to certain preparations of pork; and he further ascertained from the butcher who had supplied the meat that others among his customers, and several members of his own family who had partaken of the pork which had poisoned the girl, had been ill also, and all very much in the same way. Indeed, so many of his customers had suffered that he stopped the sale of this particular parcel of pork. Fortunately some fragments of the carcase had been preserved, and in this Zenker found multitudes of living encysted *Trichinellæ*. Henceforth trichinelliasis took its place among well established diseases, and a powerful stimulus was given to Virchow and Leuckart to continue the attempts they were then making to work out the life-history of the parasite; this, as we have seen, they succeeded in doing. From all parts of Germany and from other countries evidence of the truth of Zenker's conclusions, and the high practical value of his discovery rapidly accumulated. Since that time from North Germany alone we have the records of over a hundred epidemics of trichinelliasis. From America and from other countries we have similar records. So that at the present day trichinelliasis has come to be regarded as a very real danger to certain populations, and one against which many sanitary regulations have been devised.

*Symptoms.*—These, of course, will depend on many circumstances; upon the number of encysted *Trichinella* swallowed, upon individual idiosyncrasy, upon the number of times the infection may be repeated, and so forth.

Roughly speaking, and taking a case of average severity, the symptoms of trichinelliasis are divisible into three stages—each stage corresponding to a phase in the evolution of the parasite. There are—(first) the stage of intestinal irritation, commencing a few hours after the ingestion of the diseased meat, and corresponding to the growth, development, and sexual activity of the parent *Trichinella*, and to the penetration of the alimentary canal by their brood of young or by the gravid female; (second) the stage of myositis, characterised by severe muscular pains and irritative fever, and produced by the injury done to the muscles by the migrating *Trichinella* embryos; and (third) the stage of subsidence, corresponding to the encystment of the larval *Trichinella* and gradual subsidence of the myositis. In some, particularly in severe cases, these stages are well defined. In others, again, particularly in cases of mild, or of mild and sustained infection, they are not well defined—vague rheumatoid pains being, perhaps, the only evidence of trichinelliasis.

In an attack of trichinelliasis of moderate severity the symptoms commence within a few hours, or, at most, within a day of the ingestion of the trichinellised meat. There is early evidence of more or less violent intestinal irritation—vomiting, diarrhoea, foul tongue and breath, and colicky pains, accompanied perhaps with cramps and cold extremities. So severe may these symptoms be that they have often been mistaken for cholera. A large dose of uncooked trichinellised meat is more likely to be followed by such symptoms than a smaller dose of partially cooked meat in which, it may be assumed, many of the *Trichinella* have been destroyed. The intensity of the intestinal irritation is, however, no guide to the danger of the case; for the very severity of the vomiting and purging is the means of expelling many of the parent *Trichinella* before their young are born and have penetrated the intestinal walls. Cases, therefore, which at the outset are attended with little or no diarrhoea or vomiting may be quite as dangerous in the long run as those with violent choleraic symptoms.

About the ninth or tenth day from infection, diarrhoea perhaps still persisting, the characteristic pains in the muscles set in, and gradually increase in severity. The muscles become swollen, hard like pieces of india rubber, and very tender to the touch and on being put into action. Fever, too, is lit up by the myositis, and may run high—even up to 106° F., usually, however, it is about 102° or 103°, with slight morning remissions. Movement causes pain, and the functions of many important muscles are seriously interfered with. Thus, respiration may be affected by implication of the diaphragm and intercostals, mastication, speech, and deglutition by implication of masseters, tongue, pharyngeal and other muscles; phonation, by implication of the laryngeal muscles; expression, by implication of the facial and orbital muscles, and the pain of moving

them. Standing, locomotion, movement of the hands and arms, are all very painful—sometimes impossible. The flexor muscles are especially affected. At this stage the patient lies in bed with his limbs maintained in a state of semiflexion, or in such position as entails a minimum of pain—just as in severe rheumatism.

In most cases about the eighth day the face, particularly about the eyelids, becomes puffy and œdematous; sometimes there is chemosis. This disappears in a few days. Later, however, about the fourth or fifth week, a much more extensive œdema occurs in 90 per cent of serious cases. It affects the limbs, often the trunk, neck, and face—usually sparing the genitals. It may come and go. This œdema is sometimes very great, more extensive even than that of acute nephritis.

Profuse perspirations, often accompanied by a miliary eruption, are a usual symptom; beginning with the incidence of the myositis they may not cease to recur till convalescence has commenced. Pruritus may be troublesome in the earlier stages; later the skin may be covered with acne, pustules, or boils.

Wasting is very marked in severe cases; in fact all the symptoms of the “typhoid” condition may be presented. The tongue becomes dry, the pulse frequent; prostration may be great, and stupor marked. Not infrequently there is delirium, and nearly always in the adult there is insomnia—doubtless dependent on the pain in the muscles. Children are, on the contrary, always somnolent.

In many cases signs of bronchitis, of hypostatic congestion of the lungs, or of pneumonia set in. Much fluid accumulates in the air-passages owing to debility and to the inability of the inflamed muscles of expiration to produce effective coughing.

So the case goes on till about the fifth or sixth week, when convalescence may be looked for. The myositis gradually subsides, and in the course of a few weeks the patient is well again. Sometimes convalescence sets in earlier; on the other hand, the case may drag on for two or three months.

Death has occurred in rare instances in the first stage of the disease, from the collapse produced by choleraic purging. Generally the fatal event does not take place till the height of the myositis in the fourth or fifth week. It is usually the immediate result of asphyxia brought about by a high degree of myositis in the diaphragm and intercostal muscles; bronchitis and pneumonia, of course, add very much to the danger. Death may occur at a later stage from some complication, such as bed-sore, pneumonia, marasmus, or general asthenia. Intestinal hæmorrhage and diarrhœa are also occasional causes of death.

Since T. R. Brown, in 1897, first called attention to the blood changes in this disease, numerous cases shewing most extreme grades of eosinophilia have been recorded. The leucocytes in the one hundred recorded cases have varied from 5300 to 28,000 per c.mm., the eosinophils from 1·2 per cent to 86·6 per cent—the average leucocyte count being about 15,000 and the average eosinophil percentage about 30.

According to Schleip, who studied an epidemic at Homburg affecting 57 persons, leucocytosis is not a constant feature of this disease, being only found in severe cases, yet the severity of the leucocytosis may be taken as a sure indication of the severity of the disease. Schleip found that on the whole the eosinophils did not rise so high in mild cases as in severe cases, yet one severe case shewed only 3·2 to 5·9 per cent eosinophils of 5800 leucocytes per c.mm. The increase of eosinophils occurs very shortly after infection, before the embryos begin to enter the tissues, and lasts as long as parasites still remain in the intestine and until all the parasites have become completely encapsuled in the muscles. The red blood-corpuscles are not affected in this disease, but the blood-platelets are said to be increased in number.

The *mortality* from trichinelliasis varies in different epidemics, and evidently depends on the dose of living *Trichinellæ* ingested; being greater, *cæteris paribus*, when the trichinellised food is raw, or only lightly cooked, than when it has been thoroughly heated. Children nearly always recover. In Saxony, from 1860 to 1875, the aggregate mortality in 39 epidemics, affecting 1267 individuals, was 19, or about  $1\frac{1}{2}$  per cent. In an epidemic at Hedersleben, affecting 337 individuals, there were 101 deaths—nearly one-third.

*Diagnosis.*—Trichinelliasis is readily recognised during an epidemic of the disease when suspicion has been aroused by the simultaneous occurrence of a number of cases in a particular place, and in an associated group of individuals; but in isolated cases diagnosis is by no means an easy affair. It is very apt to be mistaken for typhoid. The distinguishing points are principally the absence in trichinelliasis of the initial headache, of the epistaxis, catarrh, and deafness, and, later, of the eruption, splenic enlargement, and serum reaction characteristic of typhoid; and by the presence of muscular swelling and tenderness, and of œdema of the face and limbs. This œdema may suggest nephritis, but it is not associated with albuminuria as in this disease it would be. From rheumatism it may be distinguished by the situation of the pain in the muscles, and by the associated disturbance of the intestinal canal. Trichinelliasis has frequently been mistaken for cholera, and, indeed, at first they may be hard to distinguish. It is said that in trichinelliasis, during the first few days of the disease, there is a peculiar feeling of heaviness of the limbs, accompanied by a sensation of tension and pain, especially in the flexor muscles, causing the legs to be dragged in walking; this symptom is said to be long antecedent to the myositis of the second stage, and is valuable as a distinction from cholera. In all cases of doubt, however, particularly in presence of an epidemic, the microscope should be used to search the stools for adult *Trichinellæ*, and any suspected food for larval *Trichinellæ*. If necessary a small piece of muscle, best from the lower end of the biceps, may be excised with the knife; the harpoon designed by Middeldorpf for this purpose produces an unsurgical wound, and removes only a very small piece of muscle.

The symptoms of trichinelliasis bear in many respects a very close



resemblance to certain forms of acute multiple peripheral neuritis, especially to beriberi—a circumstance overlooked by systematic writers, but one, especially as regards beriberi, of practical importance to the physician practising in warm climates. Both diseases occur in localised epidemics, both may be associated with œdema, both are characterised by pain and tenderness in the muscles, and both may kill by asphyxia arising from impaired power in the muscles of respiration. The principal diagnostic marks are, in trichinelliasis, the severe gastro-intestinal irritation and persistent fever; in beriberi, the early pretibial œdema, the patchy anæsthesia, the absent knee-jerks, the reaction of degeneration in the muscles, the cardiac bruits, the clean tongue, and good appetite. Trichinelliasis presents the symptoms of a myositis, beriberi of a neuritis. In all doubtful cases a blood examination should be made. The discovery of a pronounced eosinophilia in obscure febrile myalgic conditions, especially if associated with œdema and a history of gastro-intestinal disturbance, should suggest trichinelliasis and lead to excision and microscopic examination of a fragment of muscular tissue.

*Treatment.*—It is impossible to kill the embryo *Trichinellæ* after they have penetrated the intestinal walls and gained the tissues. Many drugs have been recommended with this object; they are manifestly useless and need not be discussed. But it is possible to rid the patient of many, if not of all of the parent *Trichinellæ* in the alimentary canal; and, as it has been shewn that these continue to produce embryos during several weeks, it is the duty of the physician to endeavour to get rid of as many of them as possible. His efforts in this direction should at all events be continued during the first three or four weeks of the disease. If the patient be seen soon after trichinellised food has been swallowed a quick-acting emetic should be administered at once, and its action followed up by a smart purge. Calomel up to twenty grains is said to be the most effective cathartic, the dose being repeated several times; it is credited with the power of bringing away large numbers of *Trichinellæ*. It would appear that the ordinary anthelmintics are powerless against this worm. Glycerin in large doses has been recommended; it is supposed to kill the parasites by dehydrating them. Thymol or eucalyptus oil, given in full doses as for ankylostomiasis, might prove as effective against the one worm as they are known to be against the other; these drugs deserve an extended trial in the early stages of trichinelliasis.

During the progress of the disease general treatment must be conducted on the same principles as for the continued fevers. Attention must be directed to maintaining the strength and the state of nutrition, special symptoms being treated as they arise.

*Prophylaxis.*—In Germany, where it is the custom of many people to consume uncooked preparations of swine's flesh, the systematic examination of all carcasses with the microscope is conducted by a regular service of official experts. A small piece of muscle is snipped from the diaphragm and three or four other muscles, placed on a slide, teased out with needles in one per cent solution of salt, compressed below a cover-glass, and



examined with a magnifying power of about sixty diameters. Any *Trichinellæ* the preparation may contain are easily recognised. If they are alive a slight warming of the stage causes them to move: if they are dead, they colour at once on adding aniline-blue solution to the preparation; living *Trichinellæ* do not take the stain.

Similar precautions are or were taken in other countries against imported American pork. In England such precautions are not taken, being rendered superfluous by the comparative freedom of our native swine from trichinelliasis, and the habit of thoroughly cooking pork, hams, sausages, and all similar preparations before bringing them on the table.

Thorough cooking is the best preventive of trichinelliasis; and it must not be overlooked that such things as sausage skins, lard, etc., may contain *Trichinellæ*. A safe course is to boil a joint or ham thirty-five minutes for every kilogramme it weighs.

Attention should be paid to the prevention of trichinelliasis in swine. Their sties should be kept clean and free from rats. Above all, they ought never to be fed on uncooked offal. This last precaution must be particularly attended to in large feeding and killing establishments.

#### Family IV.—Anguillulidæ

Small, mostly free-living in earth or water or parasitic in plants, rarely in animals. The œsophagus has a double swelling, and the oral cavity contains a spine or tooth. The male has two spicules and sometimes a bursa. The female pore is in the middle of the body.

This family is represented in man by two species only. They belong to the genus *Rhabditis*, the members of which are characterised by a minute filiform body tapering towards both ends, a sharp-pointed tail, and a rounded-off head carrying a terminal mouth; the œsophagus has two bulbous swellings, the more posterior of which is furnished with three folds; no tooth and no lateral line; the symmetrical double ovaries are straight; the male has two spicules, and usually a copulatory bursa with from six to ten papillæ.

*Rhabditis niellyi* (Blanchard) 1885.—(Synonym: *Leptolera niellyi* Blanchard 1885.)—Prof. Nielly, of Brest, described in 1882 a case of skin disease, characterised by a papulo-vesicular eruption attended with intense itching, in the vesicles of which an immature rhabditiform parasite—0·335 by 0·03 mm.—was discovered. The double-bulbed œsophagus was well developed, but the genital organs were quite rudimentary; evidently the animal was immature. In the same patient's blood a number of free embryo nematodes were found, suggesting that the mature parental form was lodged somewhere in the tissues and in connexion with the circulation. Possibly the embryos, after circulating for a time in the blood, escaped from the vessels and became lodged under the skin, where, on attaining a certain degree of development, they set up an irritation which induced scratching and led to their liberation.

Thus, possibly, they were placed in a position to advance further towards maturity—perhaps in the body of an intermediate host—before finally gaining access to the body of the definitive host, where they might attain to sexual maturity. Similar forms of parasitism are found in the lower animals, and it is probable that *R. niellyi* is normally a parasite of one of these.

O'Neil has described, under the name "Craw-craw" (rule p. 752)—which means in some native African languages any itching skin disease—an itching papulo-vesicular skin affection very similar to that described by Nielly, and similarly characterised by the presence of immature nematodes in the papules of the skin lesion. Geographical considerations indicate with considerable probability that the parasites observed by O'Neil were really one of the microfilariae described below, probably that of *F. persians*, which had escaped in the blood liberated in his puncturing the papules he refers to, and is merely an accidental concomitant.

**Rhabditis pellio** (Schneider) 1866. (Synonyms: *Pelodera pellio* Schneider 1866, *Rhabditis genitalis* Scheiber 1880.)—The male is 0.8 to 1.06 mm long, the female 0.9 to 1.3 mm. in length. The former has a heart-shaped bursa with seven to ten ribs on each side. The spicules are 0.027 to 0.033 mm. in length, not quite alike. The ovary is unpaired, the vulva just behind the middle of the body, the eggs measure 0.06 by 0.035. This species was found in the urine of a female patient in Hungary suffering from pneumonia and catarrh of the intestine. The nematodes were living in the vagina. *Rh. pellio* is when young parasitic in the earthworm (*Lumbricus terrestris*, etc.), and when grown up lives in moist earth. The habit of the Hungarian peasants of applying earth poultices to their bodies probably accounts for the presence of this nematode in the vagina.

#### Family V. Filaridæ

The Filaridæ are long filiform worms, very slender, and of uniform diameter, with a lipped, a papillated, or a simple mouth. (Esophagus thin, without a bulb. The tail of the male is strongly incurvated, and is furnished with several pairs of pre-anal papillæ, and sometimes an additional single unpaired pre-anal papilla, besides an uncertain number of post-anal papillæ. The male has either a single spiculum or two unequal spicula. In the female the uterus is double: ovo-viviparous. The family includes many genera, only one of which—*Filaria*—is represented among the parasites of man.

i *Filaria conjunctivæ* Addario 1885. (Synonyms: *Filaria peritoma hominis* Babes 1880, *Fil. inermis* Grassi 1887, *Fil. apapillocephala* Condorelli-Francaviglia 1892.) This worm is properly a parasite of the ass and horse. The female alone is known. It is about 16 to 20 cm. long by 0.5 mm. broad, white or brownish, and slightly flattened. The cuticle is ringed. The mouth is terminal and simple; the vulva is placed close behind the mouth. The species is ovo-viviparous, the more

mature embryos being free at the lower end of the uterus. These are rounded anteriorly, gradually tapering to a pointed tail posteriorly, and measure 0·35 by 0·005 mm. Neither the male worm nor the life-history of the parasite is known. *F. conjunctiva* has been found in man, in an immature state, only three times, namely, once in the eye, once encysted in the gastro-splenic omentum, and once encysted in the ocular conjunctiva.

ii. *Filaria oculi humani* v. Nordmann 1832.—(Synonym: *F. lentis* Diesing 1851.)—Under this name are probably included several species of minute filariæ which, from time to time, have been found either in the crystalline lens, or in the vitreous or aqueous humours. Similar parasites are found in the lower animals; it is probable that those which have been found in man are normally parasitic in beasts. Their zoological characters and pathological effects are equally unknown. It is probable that some species described under this name are identical with *F. conjunctiva*.

iii. *Filaria restiformis* Leidy 1880.—A nematode, 66 mm. long and 1·5 broad, passed from the urethra of a male in Virginia.

iv. *Filaria hominis oris* Leidy 1850.—A nematode, 140 mm. long and 0·16 broad, said to have come from the mouth of a child.

v. *Filaria labialis* Pane 1864.—Like the preceding two cases this rests upon an isolated instance, in which the worm was taken from a pustule in the lip of a man at Naples. It had a length of 30 mm. The mouth had four papillæ.

vi. *Filaria equina* (Abildg.) 1789. — (Synonyms: *Gordius equinus* Abildg. 1789, *Filaria equi* Gmelin 1789, *Hamularia lymphatica* Treutler 1793, *Tentacularia subcompressa* Zedder 1800, *F. papillosa* Rud. 1802, *F. hominis bronchialis* Rud. 1819, *F. hominis* Dies. 1851, *Strongylus bronchialis* Cobb. 1879.)—Body white and thread-like, cuticle finely ringed. The male is 60 to 80 mm., the female 90 to 120 mm. long. This is normally a parasite of the horse and ass, living in the body-cavity, from whence they spread through the host. They have been found in nodules in the lungs of man.

vii. *Filaria romanorum orientalis* Sarcani 1888.—Observed in the blood of a Rumanian; it had an alimentary canal and well-developed reproductive organs. It measured 1 mm. in length and 0·03 in breadth.

viii. *Filaria killimariæ*<sup>1</sup> Kolb 1898.—Several females were found in the abdomen of a Kitu warrior, with mouth papillæ similar to those of *F. medinensis*.

ix. *Filaria medinensis* (Velsch) 1674.—(Synonyms: *Vena medinensis* Velsch 1674, *Dracunculus persarum* Kämpfer 1694, *Gordius medinensis* L. 1758, *Filaria dracunculus* Bremser 1819, *F. æthiopica* Valenciennes 1856, *Dracunculus medinensis* Cobbold 1864. The Dracunculus, Guinea-worm, or Dragonneau) (Fig. 192).—This parasite is endemic in many parts of India, in Persia, Bokhara, Turkestan, Arabia, along the

<sup>1</sup> This is probably a young form of *Fil. medinensis*, Arch. f. Schiffs- u. Tropenhyg. ii. 1898, p. 28.

coasts of the Red Sea, in tropical Africa, and in one or two spots in the tropical parts of South America. In some of these places at certain seasons of the year nearly half the population is affected.

Although as a rule only one worm is present at a time, in countries where the parasite is very prevalent two, three, or four are not uncommon, and cases are on record in which as many as thirty coexisted in one person.

Only the female worm (Fig. 192) is well known, measuring 500 to 800 mm. in length and 0.5 to 1.7 in breadth. Her habitat is the subcutaneous and intermuscular connective tissue. Here, unconsciously to the host, she attains a great length. Some specimens measure as much as six feet, others again not more than one foot, three feet may be stated as an average length. The breadth is about one tenth of an inch. The head end of the worm is slightly tapered down, and then abruptly truncated. The mouth is terminal, and surrounded by two large and four smaller papillae. The body is white, faintly transversely striated, uniformly cylindrical, firm, very extensible, and having a breaking strain of about eleven ounces. The tail terminates abruptly usually in a small, sharply bent hook. The alimentary canal, thrust to one side and compressed by the gravid uterus is a fine tube which runs backwards from the mouth to near the tail, where it atrophies, without opening externally, by merging in the musculo-cutaneous body-wall. The vagina opens near the mouth, just outside the circle of papillae. The uterus runs from head to tail as one continuous and, relatively, enormous tube packed with millions of free embryos. Leiper has recently found the male forms in the muscles of an experimentally infected monkey. They are small, measuring 22 mm. in length. They have five pairs of post-anal papillae.

The process by which the embryo *dracunculi* quit the body of the parent worm and that of their human host is an interesting one, and has a very practical bearing on treatment. When the parent *dracunculus* approaches maturity, she begins to move slowly through the tissues, head first, and, in 99 per cent of cases, in a downward direction until her head arrives at foot, ankle, or leg. The head then drills a small hole in the dermis, sparing the epidermis.



FIG. 192. *Dracunculus medietatis*. (Nat. Hist. Mus., London.)

Over this hole a bulla forms, probably induced by the irritating properties of some secretion or discharge from the worm. In the course of a few days the bulla ruptures, disclosing a small superficial ulcer with the above-mentioned minute hole in its centre. Sometimes, on rupture of the bulla, though this is by no means usual, the head of the worm is seen protruding from this little hole. If now, whether the head protrude or not, a little cold water be poured on the limb in the vicinity of the dracuncular ulcer, a minute quantity of a whitish fluid is presently seen to well up from the central hole; or a small tube, at first pellucid, then white, is seen to be slowly extruded from this hole to the extent of about half an inch or even more. Suddenly this little tube ruptures, its contents being spilt over the ulcer. The whitish fluid alluded to is part of the uterine contents, and the little tube is part of the uterus itself, which the worm, stimulated by the water poured on the limb, forces as a prolapsus through what may be her mouth. That this is what takes place is proved by a microscopic examination of the fluid referred to, which consists, on the addition of a little water, of a mass of seething, wriggling dracunculus embryos. This discharge, with or without visible prolapsus of the uterus, is repeated at short intervals. In the course of about a fortnight the worm has emptied her entire uterus. She is now ready to quit her host; sometimes she will do so spontaneously, generally she can be readily removed by gentle and intermittent traction renewed at intervals during a day or two.

The reason why instinct leads the dracunculus to descend to the foot or ankle before beginning to empty her uterus is obvious. These are just the parts of the body which, in a warm climate and in natural conditions, are most likely to be brought in contact with water. The reason why the extrusion of embryos is provoked by contact of the limb with water is equally obvious, for the next step in the development of the embryo is made in this element. It is true that the dracunculus sometimes reaches the surface at other points of the body, but such an event is comparatively rare.

The embryo dracunculus (Fig. 193) (0.6 by 0.0175 mm.) is a long, transversely striated animal, provided with a slender tail occupying about two-fifths of the entire length. A rudimentary alimentary canal and two curious little sacs (Fig. 194) placed *vis-à-vis* at the base of the tail are readily made out. The body of the embryo is not cylindrical; it is distinctly flattened. The little animal swims about in the water very actively, and can be kept alive, especially in muddy water, for some days.

Its next step in development, as first pointed out by Fedtschenko, is made in a fresh-water copepod of the genus *Cyclops* (*C. strenuus*, *C. bicuspidatus*, *C. viridis*, and *C. quadricornis*), whose body-cavity it enters by penetrating the cuticle, or it may be by the mouth. In the *Cyclops* the young filaria undergoes a metamorphosis which is completed in from two to five weeks, according to the temperature. In this condition it is believed that the microfilaria or larva is transferred to the human

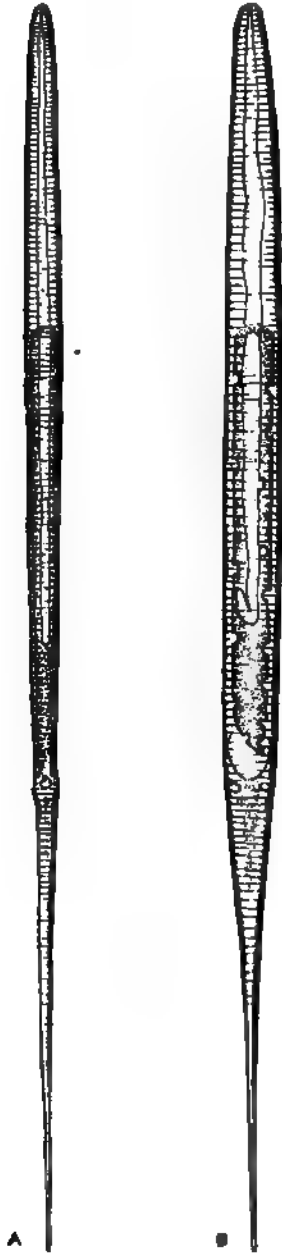


FIG. 193.—Larva of *F. madinensis* ( $\times 250$ ).  
A, ventral view, B, front view.



FIG. 194.—*F. madinensis*, showing lateral caudal sacs partially everted (highly magnified).



stomach in drinking-water. It is conjectured that the *Cyclops* is therein digested; and the parasite, being thus set free, penetrates the alimentary canal. Impregnation probably occurs in the connective tissues of the host. The parent worm takes about a year to reach maturity.

Fedschenko's experiments with embryo guinea-worms, procured in the way described above, have been frequently repeated with *Cyclops* from ponds in the neighbourhood of London. Should more than four or five succeed in making their way into a *Cyclops*, the latter in most cases dies. In these experiments metamorphosis occupied a much longer time than in Fedschenko's; for after seven weeks the first ecdysis and shedding of the tail



FIG. 195.—Transverse section of *F. medinensis*. Leuckart.

had only been completed in some of the worms, others being still provided with tails and transversely striated integument. Probably this delay was owing to the lower temperature of our English climate. The embryo guinea-worm will not enter the body of *Daphnia*. Some have asserted that the guinea-worm effects its entrance into the human host directly through the skin. The recent observations of Looss and others in the *Ankylostome* seemed to countenance this theory, which, it has been contended, is further supported by the frequency of guinea-worm in the backs of water-carriers who bear their burden in leaky skins along across the back. The following observations of Leiper militate against this view. Leiper states that for the first fortnight during the stay in the body of the *Cyclops* the microfilaria is active and changes its position; during the third and fourth weeks these movements cease, and the larva becomes quiescent. On the addition of a little 0.2 HCl, representing the acidity of gastric juice, the *Cyclops* is killed, but the microfilaria resumes its former activity. The latter casts its cuticle, and seeks a weak spot in the chitinous armour of the *Cyclops*, through which it makes its escape. Other specimens not exposed to the acid lived for some weeks in the *Cyclops*, and died soon after their host died. Leiper succeeded in communicating guinea-worms to monkeys by administering to them guinea-worm-infected *Cyclops*. His experiments are still in progress, but in one of his monkeys, which died of tuberculosis six months after the administration of the infected *Cyclops*, several male and female worms, immature, it is true, but apparently identical in structure with guinea-worms, were found in the connective tissue of the trunk and limbs.

Duke says that the appearance of a guinea-worm is usually preceded by a transient urticarial eruption often accompanied by vomiting. Beyond this, and the occasional feeling as of a cord below the skin, and

the bulla and ulcer as before described, the worm, if not interfered with, gives rise at first to no symptoms. Should unintelligent attempts at premature extraction lead to rupture of the parasite, the consequent extravasation of millions of embryos and the fluid in which they swim into the tissues is almost sure to give rise to violent constitutional disturbance—to abscess, sloughing, and similar local troubles.

This worm, like other members of the *Filaridæ*, causes an increase in the number of the eosinophil cells of the blood. The average percentage of eosinophil cells in twelve cases recorded by Powell and Balfour was 13·6, with individual counts varying from 4·7 to 36·6; the total leucocyte count remained about normal.

*Treatment.*—When she first shews herself the worm should be left alone and carefully protected by frequently renewed water-dressings. The parts ought to be douched several times a day with cold water to encourage parturition and uterine extrusion. When she is quite empty and begins spontaneously to emerge, her exit may be facilitated and accidental rupture prevented by rolling the body, as it emerges, on a piece of wood such as a match. Injudicious attempts to wind the worm out before she has emptied herself are to be deprecated, as they are nearly sure to end disastrously. If the entire worm can be made out distinctly coiled up just under the skin, she may be removed through a small incision, a loop being hooked up with a finger, whilst the surrounding tissues are carefully kneaded. Lately, injections of solution of perchloride of mercury (1 in 1000) into the track of the worm, injecting it as soon as the parasite begins to irritate the skin, have been advocated. One injection suffices. The worm is killed and is said to be absorbed like a piece of aseptic catgut. Recent observations seem to establish the value of this treatment.

Occasionally the guinea-worm fails to penetrate the skin or dies at an earlier stage of development. The worm in this case becomes cretified, and sometimes may be felt as a hard, convoluted cord under the skin of the leg. Such cretified worms do no harm, and ought not to be interfered with.

### FILARIA SANGUINIS HOMINIS

This term is applied to the free hæmatozoan embryos of various species of filarial parasites whose parental forms lie in the tissues, lymphatics, or blood-vessels, and whose young circulate in the blood of man.

From the date (1872) of Lewis's discovery—that the blood of man occasionally contains these embryo parasites—up to the last few years, it was supposed that there was only one such species of blood-worm. But at the present moment there are at least four different and well-authenticated species of *Filaria* recorded either as adults or as larvæ which pass their larval stage in the blood of man, each probably having its own special pathological relations.

There has been considerable difficulty in associating the larval forms with their parents. At present we are ignorant of the larval forms of the two genera, *F. magalhæsi* and *F. volvulus*, whilst the parent forms of *F. powelli* are unknown. The question of nomenclature presents another difficulty. In many cases the larval form was the first to be described and named. *F. nocturna* was described and named thirteen years before the parent form *F. bancrofti*, yet it is the parent form that we must regard as the species, and its name must be the specific name. Le Dantec (431) has suggested that in common parlance we should speak of the adult as the filaria, the larva as the microfilaria. If this could be done we should speak of the *F. nocturna* as the microfilaria of *F. bancrofti*; but for the present, however, such names as *F. nocturna*, *F. perstans*, etc., are too deeply embedded in medical literature to be eradicated.

The following is a list of the Filariæ whose larvæ live or are believed to live in the blood of man :—

Adult Form	Larval Form.
<i>Filaria loa</i>	<i>Filaria diurna</i>
<i>Filaria perstans</i>	<i>Filaria perstans</i>
<i>Filaria bancrofti</i>	<i>Filaria nocturna</i>
<i>Filaria magalhæsi</i>	?
<i>Filaria demarquayi</i>	<i>Filaria demarquayi</i>
<i>Filaria volvulus</i>	?
?	<i>Filaria powelli</i>

It is very probable that many more species of such hæmatozoa will be discovered hereafter. It would seem that the human blood, as well as the blood of many of the lower animals, especially of birds, is a fitting nursery for the young of an extensive fauna.

It is of the utmost importance, therefore, if we would avoid hopeless confusion and advance this new departure in pathology, that the greatest care be taken to identify the different species—diagnosing one from the other as carefully as we would small-pox from measles, pathogenic from saprophytic micro-organisms, venomous from harmless snakes. It is not sufficient to chronicle in the record of a case that “filariae were found in the blood”; we must specify the species, and, if it be a new one, describe accurately its appearance and habits.

The *Microfilarie sanguinis hominis* are long, slender, transparent, gracefully formed, snake-like organisms which, when seen under the microscope in newly drawn blood, exhibit a remarkable activity in coiling and uncoiling themselves, in wriggling and lashing about in incessant and rapid movement among the corpuscles. They remain alive—their movements gradually slowing down, however—for days on the slide, provided the blood be kept from drying up and at an ordinary temperature. Unless possessed of considerable experience it is difficult for the observer to arrive at a diagnosis of any particular specimen of microfilaria when it is first mounted on the slide; but, as movement slows down, diagnosis of species is by no means difficult if the following points be attended to :—

1. The presence or absence of periodicity in the appearance and disappearance of the embryos in the blood; and, if periodicity detected, its mode. Thus, the larvæ of one species of filaria (*F. bancrofti*) appear during the day, disappearing during the night; those of another species (*F. bancrofti*, Lewis's filaria) appear during the night, disappearing during the day; whilst those of two species (*F. perstans* and *F. demarquayi*) are constantly present both by day and by night.

2. The presence or absence of a sheath enclosing the worm. Thus *Microfilaria diurna* (the larva of *F. loa*), *Microfilaria nocturna* (the larva

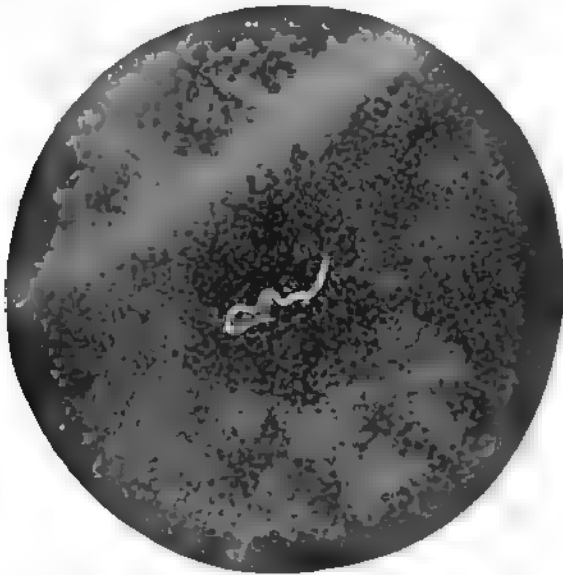


FIG. 196.—*Microfilaria nocturna* ( $\times 160$ ). From a photomicrograph by Mr. Andrew Pringle.

of *F. bancrofti*), are enclosed in long, trailing sheaths, whereas the larvæ of *F. demarquayi* and the larvæ of *F. perstans* are, so to speak, naked.

3. The shape and characters of the head and tail ends of the embryonic worm. Is the former provided with an armature, and if so, what is its character and appearance? Is the tail acutely pointed or abruptly truncated, and what is the length of the taper running up to the tail?

4. Accurate measurements of length, breadth, and other features.

5. Character of movements: lashing and stationary as in *Microfilaria diurna* and *Microfilaria nocturna*, lashing and locomotor as in the larva of *F. perstans*.

6. Associated pathological conditions if such be present.

7. Country in which the parasite was acquired.

8. Zoological characters and exact seat of any parent worm which may be found.

If attention be given to these points a correct diagnosis can be arrived in most instances.

*Technique.*—To ascertain the presence or absence of microfilariæ in the blood of man or animal the most rapid and, at the same time, most trustworthy method hitherto employed is the following, which has the additional advantages of not entailing microscopic examination until such time as may suit the convenience of the observer; moreover, dealing as it does with a comparatively large quantity of blood, it is sure to reveal the parasites if any be present and free in the circulation. The blood is procured in the ordinary way from a finger in man, or, in the case of the lower animals, from any part not covered with hair. When a large drop has welled up from prick or incision the entire amount is transferred to a glass slip by dabbing the centre of this on the blood. The blood is then spread out on the slip with a needle in a fairly uniform film, extending over an area of about one inch by one inch and a half. The slip is then laid on its uncharged surface till dry. The blood may be stained as soon as it is dry; or the slip may be labelled and packed away till a more convenient time. The blood is best stained by immersing the slide for about an hour in a very weak watery solution of fuchsin, or two drops of the saturated alcoholic solution to the ounce of water; or, more quickly, by a 2 per cent solution of methylene blue. If the blood be found too deeply stained, it may be decolorised by washing for a few seconds in a weak solution of acetic acid, three or four drops to the ounce of water. It may then be examined wet or dry, with or without a cover-glass. A magnifying power of sixty to eighty diameters suffices to shew the microfilariæ, which, with certain white blood-corpuscles, are the only stained objects in the field. Rapidity and thoroughness are secured by using a mechanical stage. The unknown and possibly varying degrees of shrinking which the microfilariæ undergo when dried in a "smear," or when submitted to staining or to other fluids, may account for some discrepancies in the measurements given by different observers.

To study the movements and anatomy of the microfilariæ slides of fresh blood must be used. Ordinary wet preparations are made, care being taken that they are not too thick; the film should be no deeper than the layer of corpuscles. If the examination is to be prolonged, or if it is to be renewed at intervals during several days, the slides had better be coated with vaseline. Search should be made for the microfilariæ with the low power mentioned; when they are found they can be centred and examined with higher powers. To see the sheath a magnifying power of 100 diameters suffices; to make out the structure of the head and the spots a good condenser and an immersion-lens are necessary, a moribund microfilaria in a field free from corpuscles being selected for study.

x. *Filaria loa* Guyot 1778.—(Synonyms of adult: *Filaria oculi* Br. et v. Ben. 1859, *Dracunculus oculi* Diesing 1860, *Dracunculus loa* Lebbold 1864, *Filaria subconjunctivalis* Guyon 1864. Synonyms of larva: *Filaria sanguinis hominis*, var. *major* Manson 1891, the larval

form is *Microfilaria diurna*, formerly called *F. diurna*.)—Wurtz and Penel found in the body of an African, who had suffered from *Microfilaria diurna*, thirty specimens of *F. loa* in the subcutaneous tissues of the limbs. They had apparently been moving actively about through the tissue. The males measure from 25 to 30 mm. in length by 0·3 mm. to 0·35 in breadth. They are white, slightly translucent, and tapering at each end, with a simple mouth, a slightly indicated neck, and incurved tail, and two rather short unequal spicules. The chitinous integument is sprinkled over with numerous hemispherical bosses in both sexes. There are three pairs of very large pre-anal and two post-anal glands. The females are 40 mm. long and 0·425 in width. The unsegmented ova measure 0·0034 · 0·0017 mm., but as the egg segments it increases in size, and by the time the embryo is formed, coiled up in the egg-shell, it attains the dimensions of 0·005 by 0·0025. The free embryos measure 0·26 to 0·3 by 0·006 to 0·008 mm.

Excepting that *Microfilaria diurna* appears in the blood during the day it closely resembles *Microfilaria nocturna*, being sheathed, sharp-tailed, possessing a central granular aggregation, a V-spot and tail, and having very similar dimensions, oral and general movements (see "*Microfilaria nocturna*," p. 934).

The diurnal periodicity of *Microfilaria diurna* has been thoroughly made out. As regards the parasite this is an important physiological fact, and is sufficient to establish the specific independence of this microfilaria from *Microfilaria nocturna*, seeing that it implies a different intermediate host, a different life-history, and therefore a different parental form. Ordinarily *Microfilaria diurna* begins to appear in the peripheral circulation about 8 A.M., increases in number till about 12 or 1 P.M., decreases in numbers as evening approaches, and disappears for the night about 9 P.M. This periodicity has been followed during many weeks.

This worm is indigenous and confined to the West Coast of Africa, where, in many districts, it is not uncommon. It lives in the subcutaneous areolar tissue, wandering about the body, and causing, when it approaches the skin, a certain amount of localised itching and irritation, and, it is believed, the peculiar form of evanescent œdema known as Calabar swellings. It occasionally appears in the eyelids or under the conjunctiva, and there gives rise to some pain and congestion.

The life-history of *F. loa* is still imperfectly known. It is ovoviviparous in the sense that when the embryo leaves the parent it is still enclosed in the egg-shell, which now forms a sheath; considering this circumstance, its location, the characters of its embryos, its peculiar geographical distribution, and that in several instances it was found in association with *Microfilaria diurna*, it was suggested in the last edition that this was the parental form of *Microfilaria diurna*. Since that time evidence tending to shew that this conjecture is correct has been accumulating, but, even now, it cannot be said that it is absolutely established.

A considerable number of instances are on record in which *Filaria loa*



been seen in the eye, but in which *Microfilaria diurna* was absent from the peripheral circulation. In yet other cases *Microfilaria diurna* been found in the blood, but *Filaria loa* had not shewn itself in the

And in many cases of the Calabar swellings, alluded to as probably caused by *Filaria loa*, neither *Microfilaria diurna* nor *Filaria loa* were found. Conversely, however, in now not a few instances, *Filaria loa* and *Microfilaria diurna*; Calabar swellings and *Microfilaria diurna*; Calabar swellings and *Filaria loa*; in at least two instances, *F. loa*, *Microfilaria diurna*,

FIG. 197. — *Filaria loa* (nat. size). Logan.

Calabar swellings have concurred in the same individual. The appearance of *F. loa* in a case of *Microfilaria diurna* infection is easily explained; for although *F. loa* may be present in large numbers in the connective tissues, and although it is evidently given to wander about the body, the chances of its traversing the subconjunctival connective tissue, the only place in which it could be seen and recognised, must be small indeed. But it is difficult to understand how *Microfilaria diurna* could be absent from the peripheral circulation in cases where *F. loa* has been seen in the eye or Calabar swellings are frequently recurring in different parts of the body, if *Microfilaria diurna* be indeed the young of *F. loa*.

The explanation is not evident; nevertheless it is true that, in at least one observed instance, pregnant *F. loa* shewed itself at one time in the eye without concurrent *Microfilaria diurna* being discovered in the blood; and yet seven years afterwards *Microfilaria diurna* was found in the peripheral circulation. A lady who had resided in West Africa for several years left that country and never returned to it. On her arrival in England a mature gravid *F. loa* was removed from her eye. At the time of the operation her blood was carefully and critically examined for *Microfilaria diurna*, but not a single example was discovered. Seven years later, several *F. loa* having been extracted from the eyes and eyelids in the interval, this lady's blood was again examined, and was then found to be swarming with *Micro-*

FIG. 198. — *Filaria loa* (magnified). From a photograph by Mr. Andrew Pringle.

*ia diurna*. She was kept under observation for several months, and although no additional *F. loa* were seen, the *Microfilaria diurna* was always present in the blood when this was examined during the daytime.

Why these embryos were not present some years before is difficult to explain. Their absence at that time and subsequent presence suggest that *Micropharus diurna* may not get access to the blood immediately at its birth. Hence their absence, it may be temporary, in many cases of undoubted *F. loa* infection and of Calabar swellings. It is more than probable that *F. loa* frequently occurs in large numbers in the body, so that the removal of one *F. loa* from the eye by no means secures against the appearance of another *F. loa* in the same situation.

Wurtz and Clerc found in a case of this infection 53 per cent eosinophils in the blood.

The intermediate host is unknown. Possibly it is a blood-sucking dipterous insect—*Chrysops dimidiatus*, the "mangrove fly" which abounds and is very troublesome and voracious, on some of the West African rivers (cf. p. 177). Species of *Anopheles*, *Culex*, *Glossina*, and *Tsetse* are also suspected.

**Treatment.** Excision. It is the custom among certain tribes of negroes to drive it from the eye by placing a few grains of salt in the conjunctival sac; sometimes they remove it by means of a sharp thorn used as a needle.

**Calabar Swellings.**—This name is applied to a peculiar form of transient and localised oedema, common in Calabar, and at one time supposed to be peculiar to that part of Africa. We now know, however, that these swellings occur in many other places in tropical West Africa, from the basin of the Niger to that of the Congo. In some limited districts they are very common. At one place on the upper Congo hardly a European who had lived there for over two years had escaped. The swellings occur in any region of the body, very often in the hands or arms. Sometimes they are accompanied by a feeling of soreness as if from a bruise; sometimes there is a sensation of heat or itching. Without obvious reason, in the course of a few hours an edematous swelling, some two to six inches in diameter, raised well above the surrounding surface, smooth and rounded in form, persists for a day or two, and then subsides without suppuration or other sign of definite inflammation. The swellings occur at irregular intervals of weeks or months, and persist in recurring during many years and long after the endemic area has been quitted. Their relationship to *F. loa* can hardly be doubted, but the mechanism of their production is not apparent. It has been suggested that they may be brought about by a *F. loa* discharging her embryo or excreta into the connective tissue.

x1. **Filaria perstans** Manson 1891. — (Synonyms of larva *Angiostrongylus hominis*, var. *minor*, Manson 1891, *Filaria cordi* Manson 1897, truncated variety.) The adults are found, distributed in little groups or more rarely alone, in the connective tissue or deeper fat, in the mesentery, in the pericardial fat, around the abdominal aorta, and in the suprarenal capsules. The female measures 70 to 80 mm. in length and 0.12 in breadth. The male is more rarely met with. It measures 45 by 0.06 mm., the tail is greatly coiled, with a large apicule, and the

pairs of pre-anal and one post-anal pair of papillæ. A distinctive mark is supplied by the bifid tail.

The microfilaria of *Filaria perstans* is considerably thinner and shorter than *Microfilaria diurna* and *Microfilaria nocturna*. It is further distinguished from them by not possessing a sheath, by its truncated tail, by the absence of a central granular aggregation, by the characters of its oral armature, by its movements, and by the absence of periodicity. Its average dimensions may be set down at 0·23 mm. by 0·0045 mm.; but as it has the habit of extending and attenuating, and of shortening and thickening itself as it travels about in the blood, an approximate and average measurement only can be given. As already mentioned it has no sheath. The thickest part of the body is about one-third of the distance behind the head; from this point it gradually slopes off to the abruptly truncated tail. There is no conspicuous central granular aggregation. The head end is armed with a minute, exceedingly delicate filiform spine set on what looks like a papilla. This spine and papilla are constantly and rapidly protruded and retracted. In addition to effecting very active wriggling movements, *F. perstans* travels about, often very rapidly, among the corpuscles, the attenuation and extension of its body facilitating its peregrinations. At no time very numerous—sometimes only three or four on a slide, rarely as many as twenty or thirty—the *Microfilaria perstans* can be found as readily by day as by night. It may be associated with the *Microfilaria diurna* or with the *Microfilaria nocturna*, or with both.

Considering its remarkable locomotive habits, its cephalic armature, and the absence of the sheath which in other blood-worms acts as a muzzle, the microfilaria of *F. perstans* may leave the blood-vessels by its own efforts, and have a somewhat different life-history from the sheathed and non-locomotive filariæ. What this life-history may be is at present a matter of conjecture.

The intermediate host is unknown. *Argas (Ornithodoros) moubatu* has been suggested. Species of *Anopheles*, *Stegomyia*, and *Panoplit*es have been tried without result.

So far as known, *F. perstans* is confined to tropical Africa and Demerara. In some districts, quite two-thirds of the inhabitants are affected by it; in other districts it is not so prevalent, whilst in yet others and neighbouring districts it appears to be absent.

xii. *Filaria bancrofti* Cobbold 1877.—(Synonyms: *Trichina cystica* Salisbury 1868 (nec *Filaria cystica* Rud. 1819), *Filaria sanguinis hominis* Lewis 1872, *Filaria sanguinis hominis aegyptiaca* Sonsino 1875, *Filaria wuchereri* da Silva Lima, *Filaria sanguinis hominum* Hall 1885, *Filaria sanguinis hominis nocturna* Manson 1891, *Filaria nocturna* Manson 1891. Larval form: *F. nocturna*.)

The parental forms of *Microfilaria nocturna* were discovered by Bancroft of Brisbane in 1876. They live in the lymphatics of the trunk and extremities. They have frequently been encountered in recent years, the sexes being usually found in association. Sometimes

several six or seven are found together, coiled up and twisted about each other (Maitland), in other instances they appear to be stretched out in the vessel containing them. When newly exposed they exhibit active, wriggling movements, looking like short lengths of animated white horse hairs. The males are particularly active, and show a great disposition to coil. These mature filariae are long (female, 76 to 80 by 0.21 to 0.28 mm.; male, about 40 by 0.1 mm.), capillary, white, smooth, and uniform in thickness except near the head and tail, where they taper somewhat. The tail is incurvated in both sexes, spirally twisted like a vine tendril in the male, which can readily be recognized with the naked eye by this feature as well as by his inferior dimensions. The tail in both sexes is blunt at the tip, measuring there 0.03 mm. in breadth. In the female (Fig. 200) the anus opens 0.28 mm. from the tip of the tail, and the vulva about 1.2 mm. (3) behind the mouth. In both sexes the head is club-shaped, the mouth being terminal and simple (Fig. 200). The thick lipped cloaca of the male is placed about 0.13 mm. from the tip of the tail (Fig. 200). It has been stated that he has three pairs

FIG. 200. *Filaria bancrofti*, female (nat. size). After Cobbold.

of pre-anal papillae; at least three pairs of post-anal papillae have been made out.<sup>1</sup> He has also two unequal spicules (*a*, *b*) (in length 0.6 and 0.2 mm. respectively) having rather broad, brownish coloured, chitinous bases (length, 0.17 and 0.12 mm.), from which spring long, delicate, wavy, filamentous rods. The uterus is double (Fig. 200). The alimentary canal is simple and straight. It is believed from the analogy of the corresponding blood worm of the Chinese crow—*Cirrus torquatus*—that in the higher part of the uterine tubes the differentiated embryos lie coiled up in the ova in the usual way, the ovum measuring at this stage 0.05 mm. by 0.034 mm.; that lower down the embryos have, by their incessant movements, so separated the poles of the ovum that the ovum becomes a long oval; and that still lower down, and near the vulva, the vitelline membrane has become so elongated by a continuation of this stretching process that it now constitutes the sheath of the free-swimming hæmatozoan filaria.

The young microfilariae are born into the lymph which bathes the parent worm; in this they are carried along the lymphatics, traverse the glans (should any of these intervene), and, entering the thoracic duct, thus reach the blood. It is conjectured that if their arrival occur during the night they circulate with their brethren, but if they should happen to enter the circulation during the day, after one or more rounds of the vessels, they are arrested, in certain organs to be alluded to presently.

*Microfilaria nocturna* (Fig. 201) was first discovered by Demarquay in 1863, in the fluid from a chylous dropsy of the tunica vaginalis testis.

<sup>1</sup> These numbers are given by Braun. Penel says the matter is as yet undecided.

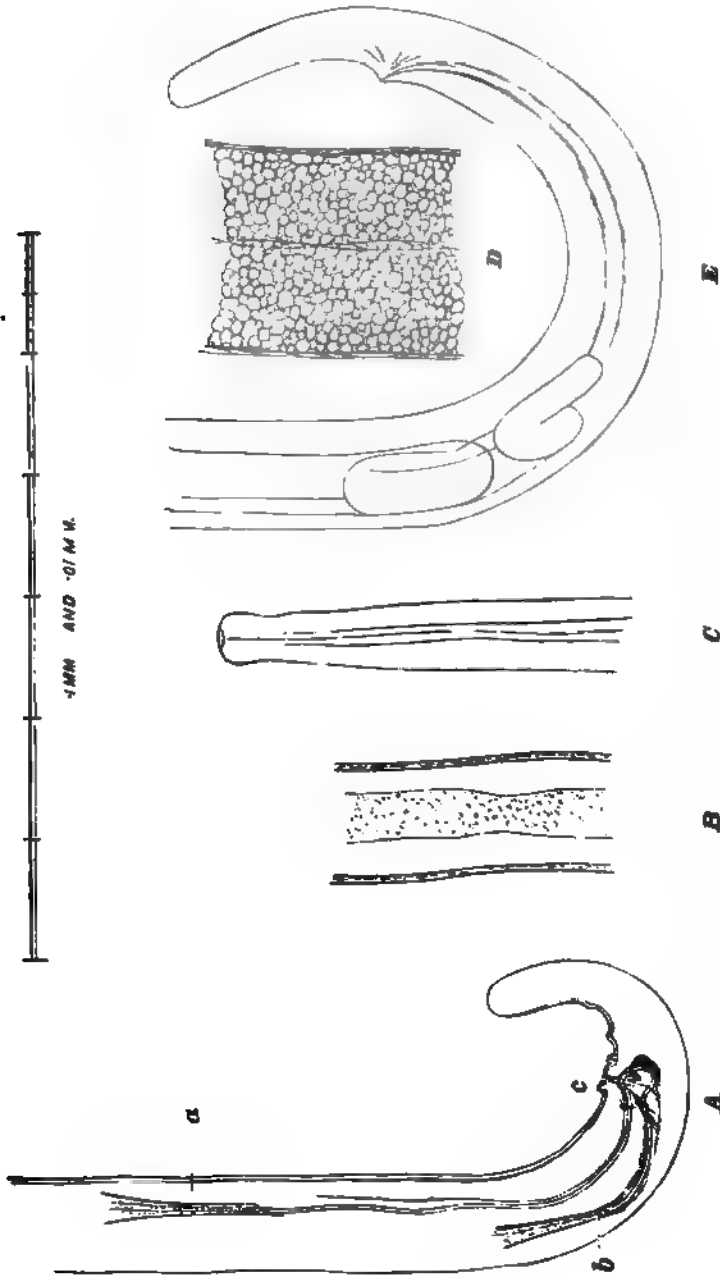


FIG. 310. — *Plasmodium bancrofti*, magnified. A, tail of male; B, constriction at junction of intestine and oesophagus; C, head and neck; D, fragment of female, showing uterine tubes; E, tail of female. a, long; b, short apicula; c, cloaca.

in 1864, it was found in chylous urine by Wucherer, and, as already mentioned, in the blood by Lewis in 1872. Since that time it has been found in the blood and in morbid discharges in many countries from England on one side of the equator to Australia on the other. Its geographical range is therefore an extensive one. Practically, however it may be said to be a prominent pathological factor in tropical and sub-tropical countries only, and in these more especially in particular districts. In some places (for example, Amoy, Batin) it is to be found in quite 10 per cent of the population, in other places (for example, Cochinchina) as many as 30 per cent, or even 50 per cent (Samoa). Speaking generally its rarity or its frequency seems to depend on the presence of particular

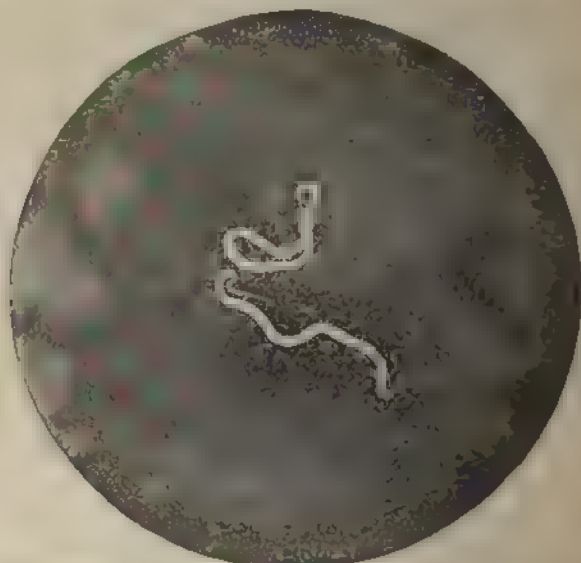


FIG. 201.—*Microfilaria nocturna* (x 100). Photomicrograph by Mr. Andrew Fritzie.

species of mosquitoes, and on the habits of the natives with regard to their clothing, domestic condition, and occupations. It is probable that the degree of prevalence of elephantiasis is an indication of the degree of prevalence of *Microfilaria nocturna* among the natives of a country.

The general features of the embryo-hematozoan stage of this microfilaria have already been sufficiently described. Its special characteristics are—its dimensions a little over or under 0.3 mm. by 0.008 mm.; a sharp-pointed tail having a taper of about one-fifth of the entire length of the animal, an ill-defined granular aggregation, usually visible for a short distance around the axial line of its body about the junction of the middle and posterior third, which by particular methods of staining can be shewn as if a hollow viscus; a minute, luminous V-shaped spot (probably connected with a rudimentary excretory system), with its apex



opening on the surface of the body, and placed a short distance behind the cephalic extremity; a similar but much smaller spot near the end of the tail; and the cephalic armature. The latter consists of a retractile and protractile six-lipped prepuce, covering and uncovering a thick, hemispherical proboscis, which is further provided with a minute, filiform, protrusible, apical spine.

The microfilaria is enclosed in a delicate sheath (Figs. 202 and 203), which, being too long for it, dangles, collapsed from head or tail or from both, giving rise to the appearance of a lash. The microfilaria can be seen to move backwards and forwards inside this sheath, which, as already explained, may be the remains of the vitelline membrane of intra-uterine life. This organ subserves an important function in the life of the parasite—its object, if the expression may be used, being to act as a muzzle on the cephalic armature, and to prevent the parasite from using these formidable weapons prematurely; for if by means of them it penetrated the walls of the blood-vessels of the human host, and thereby escaped into the perivascular tissues, it would be out of the way of its intermediate host, the mosquito, and have no chance of continuing its development.

*Microfilaria nocturna* begins to appear in the peripheral circulation about five, six, or seven in the evening, and thereafter gradually increases in numbers up to midnight. After midnight the numbers diminish in the same gradual way as they had increased during the earlier part of the night. By seven or eight in the morning, save for an occasional straggler which may be encountered at any hour of the day, they have all disappeared. This remarkable phenomenon, which has been called "*filarial periodicity*," goes on daily and for years. It depends in some way on physiological conditions bound up with the sleeping and waking habits of the host; for if the latter sleep during the day and keep awake during the night, the filarial periodicity is correspondingly inverted. Fever and irregular habits of sleep are found to interfere with this peculiar phenomenon and otherwise to break up the regularity of its manifestations. It has been ascertained that the microfilariae, during their diurnal absence from the peripheral circulation, accumulate in the thoracic viscera, particularly the lungs and larger blood-vessels. There is no accumulation in the spleen, liver or kidney; a few may

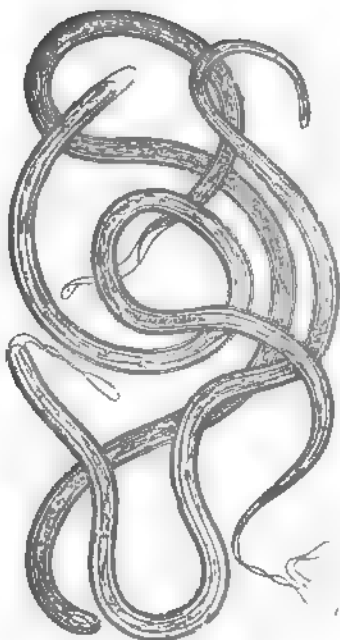


FIG. 202. *Microfilaria nocturna*, showing sheath. After Lewis.

be found in the two latter organs and also in the brain, but the vast majority concentrate in the thorax.

The number of microfilariae discoverable in the blood at any given time will depend on the degree of infection of the individual, and also on the hour at which the examination is made. Under normal conditions the numbers in the circulation, as observed from day to day in the same individual, are found to be fairly uniform; but, as the parent worms may die as the result of accident or disease, and as the stock of parent worms may from time to time be increased, in the course of years the numbers of embryos free in the blood may fluctuate—increasing, or decreasing, or disappearing altogether. In blood drawn late in the evening—ten to twelve o'clock—it is no unusual thing to find as many as 100 parasites in a single drop, sometimes as many as 500. Assuming the filariae to be uniformly distributed throughout the blood of the body, this would give an aggregate of some  $3\frac{1}{2}$  millions in every pound of blood, or 40 to 50 millions in an average-sized man. Notwithstanding these enormous numbers, their incessant activity, and their by no means insignificant dimensions, the embryo filariae do no harm whatever, and the host is as unconscious of this huge population in his vessels as he is of his blood-corpuscles.

The nocturnal habits of the filaria are an adaptation to the nocturnal habits of one or more species of mosquito, the females of which act as its intermediate hosts. *Culex fatigans*, *Anopheles rossii*, *Anopheles gambiae*, *Paraphlebotomus africanus*, *Stegomyia fuscicola* are all said to be efficient intermediaries. These insects imbibe the larval parasite when they suck in the blood of an infected subject, and thereafter the parasite undergoes a metamorphosis in the tissues of the insect. The larva leaves the stomach and comes to rest in the great thoracic muscles of the mosquito. Here they grow and develop, attaining a size of 1.5 long by 0.25 mm in breadth. They then make their way into the mouth parts, come to rest in the labium, and, like the embryo *Filaria immitis* of the dog, they make their way into man when the mosquito bites.

The principal steps of this metamorphosis consist, in the first instance, of the escape of the filaria from the sheath which, up to the time of the arrival of the worm in the stomach of the mosquito, had muzzled its cephalic extremity. This is brought about by the thickening the blood undergoes as soon as it is swallowed by the insect. The gastric juices so act on the blood-corpuscles that their hæmoglobin escapes into the serum, which thereby, assisted by absorption, is rendered more viscid, gummy, and clinging. In this state it arrests the sheath, as it were, and by fixing this enables the filaria to ram its way out. This condition and effect of blood viscid from escaped hæmoglobin are readily reproduced experimentally by chilling (not freezing) slides of blood containing filariae—by laying the slides on ice for a few hours, and subsequently warming them to 70° or 80° F. In blood so treated it is easy to observe the filaria ramming the sheath and butting their way out, head first, just as they do under normal conditions in the stomach of the mosquito (Fig 2031).

When the filaria has got rid of its sheath in this way its cephalic armature is unmuzzled, and is at once made use of by the parasite to bore its way through the wall of the insect's stomach and into the thoracic viscera, where, a few hours after the mosquito has fed, the migrated filariæ can be found in great abundance. Here for a time the parasite falls into a sort of passive pupal condition, acquiring four lips and an alimentary canal. Finally it takes to growing with great rapidity, becomes furnished with a three-lobed arrangement at its caudal end, and exhibits great activity, swimming about freely when placed in water. At this stage it travels forward into the prothorax, head, proboscis, and palpi of the mosquito. The exact process by which it enters the human host is unknown. It is believed to be during the act of haustellation. The metamorphosis takes place in from six to twenty days according to temperature. The forms intermediate between this stage (that in which, presumably, it enters the human body) and the mature worm, some three or four inches in length, found lying in the lymphatics, have not been traced.

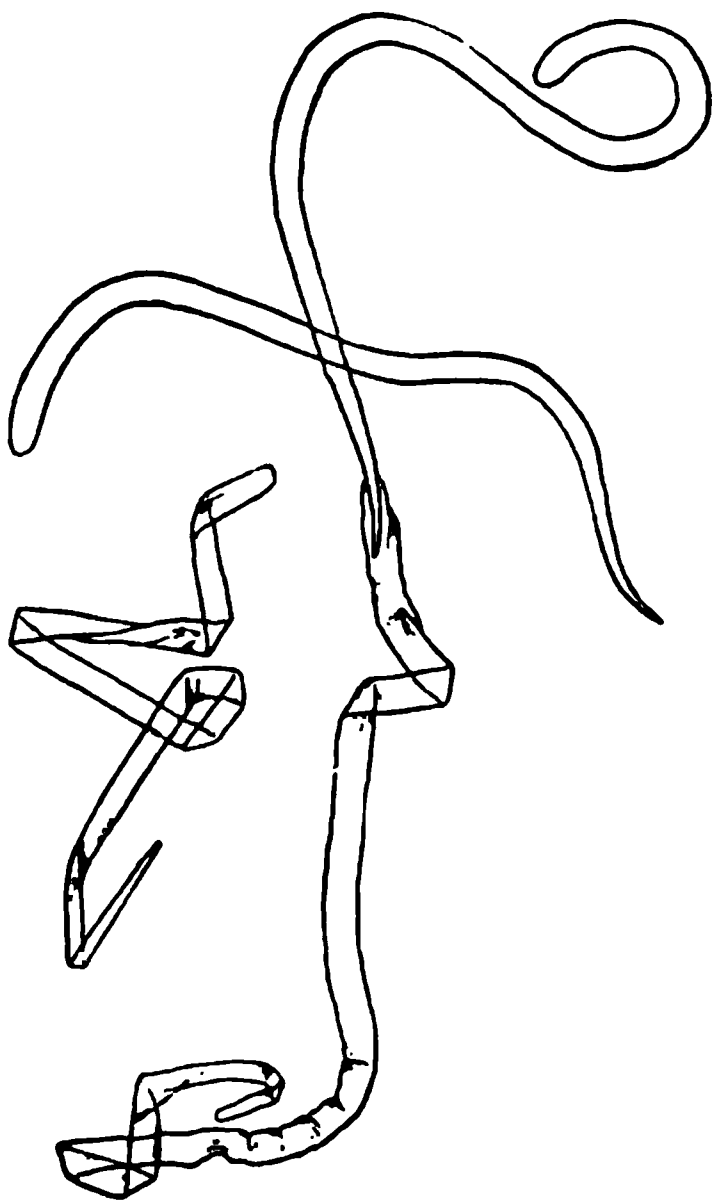


FIG. 203.—*Microfilaria nocturna* casting its sheath.

**Filariasis.**—*Microfilaria nocturna*, both in its embryonic and in its mature forms, seems to be perfectly adapted to live in harmony with its human host. In Prof. Lankester's phrase, the host is "tolerant" of the parasite. As a matter of fact, in the vast majority of instances it gives rise to no disease whatever. In some cases, however, this harmony is somehow interrupted, and then grave disease may accrue.

The red blood-corpuscles are usually but little altered in this affection, but the leucocytes shew a disproportionate increase in the eosinophil cells. This eosinophilia has a cyclical course, following the periodicity of the embryo worms in the peripheral blood—in one case, with a leucocytosis of 23,000 per c.mm., the percentage of the eosinophils during the course of twenty-four hours varied from 8 to 22, while in a second case with a leucocyte count of 10,000, the daily variation was from 3 to 15 per cent.

The endemic forms of a group of diseases—including chyluria, varicose groin-glands, lymph-scrotum, chylocele, certain varieties of lymphorrhagia, orchitis, endemic lymphangitis, and varieties of cellulitis—all depending on a varicose condition of the lymphatics, are certainly attributable to *F. nocturna*. Endemic elephantiasis arabum is probably dependent on the same

cause. For convenience the former group will be designated "elephantoid diseases," the latter "elephantiasis."

### ELEPHANTOID DISEASES

**Chyluria.** Although at long intervals cases of chyluria originating in temperate climates, and in individuals who have never visited warm countries, have been reported, the vast majority of cases of this affection occur in persons who are living in or who have lived in tropical countries. There is scarcely a tropical country in which such cases are not encountered from time to time. Brazil, Mauritius, India, China, and the West Indies might be specified as supplying many of the recorded cases.

Both sexes are liable to the disease. In the case of women its first appearance may date from a pregnancy, in the case of men very often from some unusual physical effort. In many instances the symptoms supervene without manifest exciting cause.

*Symptoms.*—The characteristic symptom of chyluria—the milky condition of the urine—appears suddenly. On passing water the patient notices the peculiar alteration in its character; or, it may be, he is seized with retention, and when relief is obtained by the catheter, or spontaneously, after some hours of suffering, it is observed that the urine is opaque, milky white, pinkish, or red like blood. It is also remarked that it contains coagula, the intravesical formation of which had caused the retention. This condition of urine may persist for a day or two, for weeks, for months, or even for years. In most cases after a time the excretion becomes normal. But ever afterwards, at uncertain intervals of weeks, months, or years, the chylous condition is liable to recur, and to persist for an uncertain time.

Usually a relapse is preceded by a dragging, aching sensation in the loins, groins, thighs, testes, and about the pelvis generally. These uncomfortable sensations may disappear with the appearance of the chyluria; but if the abnormal discharge persist for a very long time this loin ache is apt to reappear, and to have superadded to it feelings of weakness, prostration, and all the usual symptoms of anemia, including, very often, extreme mental depression. In a certain proportion of cases of chyluria the glands of the groin are found to be prominent and varicose; the lymphatics of the scrotum may be similarly dilated.

The colour of the urine and the amount of clot it contains vary in different cases, and even in the same case at different times of the day, and from day to day. In some instances the urine may be milky white; usually it has a pinkish tinge, in yet other cases it may be red like blood. The latter condition is sometimes called "hæmato-chyluria." Generally the urine passed on rising in the morning is to all appearance normal, and it is only as the day wears on that it becomes chylous. In other cases the morning urine is chylous, whereas the urine passed at some other time of the day may be quite, or almost,

clear. In some cases clots are formed in the bladder, giving rise to pain and difficulty in passing water ; in other cases the coagulum is not formed till the urine has left the body ; and in another class of cases no coagulum forms at all, or only occasionally.

Usually, if chylous urine be passed into a urine-glass, the entire mass of fluid coagulates rapidly. In a very short time the clot thus formed contracts, becoming, as it contracts, pinker or redder in colour, firmer and more fibrous in consistence ; the fluid in which it floats looking whiter and clearer in contrast. In the course of a few hours, or of a day, the coagulum contracts to comparatively small dimensions. The fluid portion of the urine has now separated into three layers-- an upper, forming a thin, greasy, cream-like layer or pellicle ; a lower, formed of scanty, dark-red sediment ; and an intermediate layer, constituting the bulk of the fluid in which the coagulum is suspended. Under the microscope oil globules and much granular fatty matter are to be found in the upper layer ; in the middle layer much molecular fatty matter and some lymph- and blood-corpuscles ; and in the lower layer a larger proportion of lymph- and blood-corpuscles, besides small clots, urinary salts, and epithelium, and, in the majority of instances, dead or slowly moving embryo filariæ. If a portion of the clot be teased up it is found to contain, enclosed in the meshes of the fibrin, lymph-corpuscles, red corpuscles, and, in most cases, a considerable number of filariæ.

To find the filariæ in the urine it is necessary to employ a low magnifying power, 50 to 80 diameters ; and to search in the sediment or in the clot. To search in newly passed urine, or in the upper and middle layers above referred to, is almost a hopeless task.

On shaking the urine up with ether it becomes clear ; on boiling it large quantities of albumin are thrown down.

Judging from a limited number of observations the filaria does not exhibit in the urine that diurnal periodicity which characterises it in the blood ; it may be found in chylous urine at any hour, irrespective of the time at which the urine was voided. So far as known, if the filaria be found in the urine it will also be found in the blood, that is, if searched for at the proper time.

Chyluria, although often an extremely debilitating disease, is seldom directly fatal. Connected, as it usually is, with the presence of mature parasites in the thoracic duct, it is liable at any moment to be complicated by serious conditions arising out of the death of one or more of these parasites. Generally no bad consequences result from the death of the parent filariæ, but there is evidence that at times such an event may be the starting-point of a septic abscess which, being located in a surgically inaccessible position, may prove fatal.

*Diagnosis.*—The presence of clots at once distinguishes chyluria from such purulent conditions of urine as are associated with pyelitis, abscess rupturing into the urinary tract, and cystitis ; and from phosphaturia, etc. Diagnosis is further aided by the discovery of filariæ in the urine and blood, by varicose conditions of the groin lymphatics, and other symptoms

of filariasis. The only condition about which doubt might be entertained is a combination of chyluria with endemic hæmaturia. The concurrence in the urine of filariæ and bilharzia ova will at once clear up the difficulty. It sometimes happens, however, that the filaria has disappeared; in such a case diagnosis may be difficult if not impossible.

**Varicose inguinal glands** are a very common effect of the presence of *F. nocturna* in the lymphatics. Both groins may be involved, usually one side more than the other; occasionally one side only is affected.

On inspection the upper part of Scarpa's triangle is seen to be occupied by a rounded, obscurely lobulated, broad-based swelling, suggesting hernia. In many instances the swelling has the appearance of being made up of two main masses—an upper, roughly corresponding to the direction of Poupart's ligament; and a lower, corresponding to the saphenous opening. These swellings, which merge into each other, may attain the size of one or two fists, or they may be no larger than a small apple or a walnut. To the touch they are doughy, obscurely fluctuating, with perhaps here and there harder kernel-like masses. In other instances the swellings are firmer, and very obscurely varicose. The superjacent skin is freely movable, but the tumour cannot be slipped over the subjacent tissues; in the recumbent position the swelling diminishes considerably; firm pressure disperses it altogether. Still keeping the palm of the hand on the affected region, if the patient be made to stand up, the swelling slowly returns, contrary to what would happen in hernia; and on percussing it the note is found to be dull, not tympanitic as in hernia. In coughing there may be a slight impulse, but this is not nearly so marked as in hernia. When taxis is made in the recumbent posture, though the swelling disappears, it does so very slowly; there is no sudden slipping up of the mass or attendant gurgling, as in hernia. It will be seen that the characters of the tumour approximate more to those of an epiplocele than of an ordinary hernia.

If a hypodermic needle be thrust into the tumour a syringe of opaque milky, or pinkish, or sanguinolent, or straw-coloured fluid can be readily withdrawn; and if the barrel of the syringe be laid aside, the needle remaining in place, the fluid will continue to drop from it for hours, and until many ounces have escaped. On withdrawing the needle some swelling may arise around the tumour, apparently from infiltration of the fluid into the cellular tissue; this, however, is quickly absorbed, and the swelling in a few hours reverts to its usual size.

The aspirated fluid coagulates rapidly. Under the microscope it is found to contain much molecular fatty matter, lymphocytes, and red blood-corpuscles, and generally, though not invariably, very active micro-filariæ.

These tumours are said by Mazaé Azéma to appear, as a rule, between the thirteenth and twentieth years, and to be apt to disappear between forty and fifty. From time to time they may be the seat of periadenitis and are then very painful. As a rule, however, beyond a sense of distension and dragging, generally much increased by exercise



and the erect posture, and then often exceedingly distressing, they are not attended with actual pain.

It is rare to meet with a similar affection of the axillary glands, although a few such cases have been recorded.

**Lymph-scrotum**, like chyluria and varicose inguinal glands, is almost a sure indication of the presence, actual or past, of *F. nocturna* in the lymphatics.

On inspecting and palpating such a scrotum it is found to be slightly or very considerably enlarged and perhaps thickened. Here and there, varying in size and number, scattered over the surface, sometimes arranged in lines or groups, herpes-like but non-inflammatory vesicles, or longer varicosities elevating and roughening the skin, are perceived. Some of the vesicles may be no larger than a pin's head; others may be as large as peas or small beans. In some cases their contents, seen through the thin skin, are milky white, in others pinkish or dark red, in yet others clear and straw-coloured.

On pricking one of these varicosities a larger or smaller quantity of fluid escapes. Sometimes only a drachm or two can be procured; usually it is an easy matter to collect many ounces, for the prick may continue to drip for hours, the lymphous fluid soiling the patient's clothes and making him very uncomfortable. On collecting a few ounces it is seen to be straw-coloured, milky, pinkish, or dark red. It coagulates rapidly, and under the microscope is found to contain much molecular fatty matter, lymph- and red blood-corpuscles and, very generally, living micro-filariae. Microfilariae are generally though not invariably present in the circulation in these cases.

This condition of scrotum may continue for many years, in some instances gradually assuming the characters of ordinary elephantiasis. Attacks of fever and inflammation recur at uncertain intervals; not infrequently these attacks lead to the formation of large abscesses; usually they terminate with a profuse discharge of the lymphous fluid from the surface of the tense, swollen scrotum. A varicose condition of the lymphatics of the spermatic cord and orchitis are common complications.

Apart from the suffering attending these attacks of inflammation, the inconvenience of the swelling, and the debilitating effects of the recurring attacks of lymphorrhagia, lymph-scrotum is not a very serious complaint. It frequently co-exists with varicose inguinal glands and chyluria. In a few instances the surgical removal of the scrotum has been followed by chyluria, and occasionally by elephantiasis of a leg.

**Chylocele.**—The tunica vaginalis sometimes contains a milky or reddish fluid exactly similar to that of varicose inguinal glands and of lymph-scrotum. Filaria embryos are generally to be found in it abundantly, as well as in the blood. The contents of the tunica vaginalis in such cases may amount to eight or ten ounces, or to a few drachms only. Very frequently in chylocele the inguinal glands are varicose; the co-existence of this latter condition with an opaque,

fluctuating swelling of a testis justifies, as a rule, a diagnosis of chylocele: more especially if filariæ are found in the blood.

The chylous dropsies of the peritoneum, chylous dropsies of the pleura, chylous diarrhoeas, and various forms of cutaneous lymphorrhagia and circumscribed inflammation or thickening of the lymphatics which from time to time have been reported, were doubtless in many instances of filarial origin, and pathologically allied to the commoner and better-known varieties of filariasis just described.

*Pathology of Elephantoid Disease.*—Seeing that these various affections often accompany or follow each other, that the characteristic chylous fluid is a feature they all have in common, that they occur endemically in the same districts, and that each is generally associated with the presence of the *Microfilaria nocturna* in the blood and in the characteristic fluid, the inference that they depend on the same cause, and this the filaria is warranted.

Autopsy has shewn that in varicose groin-glands the tumour consists of a mass of dilated lymphatics which are but part of an enormous varix extending into the pelvis and involving the thoracic duct. Two valuable autopsies of cases of chyluria associated with the filaria—one by Sir Stephen Mackenzie, the other by Curnow—revealed in both instances an impervious condition of the upper part of the thoracic duct, and enormous dilatation of that vessel below the seat of obstruction, together with a varicose condition of the abdominal, renal, and pelvic lymphatics. These facts, together with the circumstance that the milky fluid in the urine in chyluria, in varicose groin-glands, in lymph-scrotum, and in chylocele possesses all the characters of chyle plus the presence of filaria embryos in the fluid as in the blood, suggest the following hypothesis of the production of these diseases:—

In some way as yet unexplained, either by mechanical plugging by a bunch of intertwined parent filariæ, or in consequence of inflammatory conditions leading to stenosis brought about by the presence of such filariæ in the vessel, or in some other way connected with the parent filariæ, the thoracic duct becomes occluded. As a result of this occlusion there is stasis of chyle and lymph in the thoracic duct and in all its tributaries below the point of obstruction. Concurrently with the stasis there is a rise of pressure in the lymphatics of the implicated area. As a consequence of this rise of pressure, a movement of lymph sets in the direction of least pressure, that is towards the anastomosis of the lymphatic system of the thoracic duct with the lymphatic system draining the upper part of the body. The relief thus obtained will gradually extend nearer and nearer to the thoracic duct itself, and finally the contents of this vessel will partake in it. But for the contents of the thoracic duct—which include the chyle from the intestine—to reach this anastomosis they must take a recurrent course, through the pelvic lymphatics, through the inguinal and upper femoral lymphatics, through the scrotal lymphatics, and so over the abdomen and dorsal region to the upper part of the body. To accommodate

this augmented stream these lymphatics must dilate ; this, together with the rise in pressure which must accrue before the anastomosis is completed, may end in producing a varix which, should it involve the renal or vesical system of lymphatics, may by rupture give rise to chyluria ; if it include the inguino-femoral glands—varicose groin lymphatics ; if the scrotum—lymph-scrotum ; if the tunica vaginalis—chylocele.

If this hypothesis be not correct, how can the presence of chyle in the urine, in the groin, in the scrotum, and in the tunica vaginalis be explained? Chyle must come from the lacteals, and the only route by which it can reach these parts is the one described. When we tap a lymphatic varix of the scrotum or of the groin, we tap the anastomotic plexus by which the chyle, denied a route up the thoracic duct, is finding its way to the circulation.

Objection has been raised to this supposition on the ground that the abnormal substance in the urine in chyluria is sometimes sanguineous, and therefore that it must have come, in part at least, from the blood-vessels ; and impossibilities, such as perforation of the blood-vessels, have accordingly been attributed to the embryo filariæ. But in a certain proportion of cases these embryos are wholly absent from the urine and also from the blood ; and yet the so-called hæmato-chyluria persists for years. If, then, in some cases the sanguineous character of the urine arises independently of embryo filariæ, why not in all? It is a well-known fact that in the upper part of the thoracic duct the lymph is pinkish, sometimes even red ; and includes some red blood-corpuscles. This is specially noticeable in dogs which have survived ligature of the thoracic duct for some time. Manifestly the contents of this vessel, even if delayed in the vessel, continue their normal evolution towards the formation of blood. Thus, without assuming rupture or perforation of blood-vessels, the pinkish or red tinge and the red corpuscles in some cases of chyluria can be satisfactorily explained. These diseases are entirely diseases of the lymphatic system ; the blood-vessels are not engaged in them.

After obstruction of the thoracic duct has been set up by the parent filariæ it is of no consequence, so far as the production of an inverted flow of chyle and lymph is concerned, whether the filariæ live or die. A stricture of this description once produced is permanent, and continues after the cause which had given rise to it has long passed away. Hence the occasional absence in chyluria, and in the other forms of lymphatic varix described, of the embryo filariæ. In such cases the parent filariæ, after having damaged the thoracic duct, have died.

#### ELEPHANTIASIS ARABUM

Although elephantoid thickening of the integuments of the feet and legs and of other parts occasionally originates in cold climates, such an occurrence must be considered as extremely rare. In the tropics and subtropics it is otherwise. There elephantiasis is common

enough—in some places so common that a large proportion of the inhabitants are affected. For example: in parts of Travancore about every twentieth individual has elephantiasis; in some of the South Pacific Islands (Samoa, Huanine) nearly half the inhabitants are affected. These are extreme cases; but almost everywhere in the tropics this disease is more or less common. It becomes rarer as we proceed north and south; beyond the 35th degrees of N. and S. latitudes it is practically unknown.

Elephantiasis affects various regions of the body. As a rule the legs or scrotum, or both, are the only parts attacked; at times, however, the disease shews itself in the arms, in the mammae, in the female genitals, and in the scalp.

According to statistics prepared from 2081 cases occurring in India and Brazil, the following parts, alone or in conjunction with other regions of the body, were affected in the percentages stated:—Lower extremities 96·84 per cent; upper extremities, 5·86 per cent; scrotum, 2·3 per cent. The mammae were involved once in every 690 cases; the lobe of the ear once only in the entire series. No mention is made in these statistics of the disease attacking the female genitals. It would appear that in districts in which the endemic influence is very powerful the proportion of arm, scrotum, and mammae cases to leg cases is greater than in districts in which the endemic influence is milder; thus in the South Pacific Islands arm and breast cases are not infrequent.

Elephantiasis begins with an attack of lymphangitis and erysipelatoid inflammation of the integuments. Constitutional symptoms are severe, setting in with a sharp and prolonged rigor, followed by high fever, which, in the course of a day or two, generally ends in profuse diaphoresis, and often in a sort of lymphous weeping from the implicated skin. The inflammatory effusion is only partially absorbed; some thickening remains. These attacks occur at irregular intervals of weeks or months, each attack leaving the limb or scrotum somewhat larger than before, until, in the course of years, the skin and cellular tissue has become enormously and permanently hypertrophied, and an unwieldy mass, justifying its name—elephant leg,—is formed.

In the long-established disease the surface of the affected part is rough and tuberoso, the papillae pilose, warty or atrophied. At the ankle—if it be the leg that is affected—the skin is thrown into folds like rhinoceros hide, deep sulci between the folds permitting a small range of movement at the joint. The nails are rough and thick; the hairs, in parts, long and coarse; sensation is somewhat impaired; sweating is defective, and the parts are often darker than normal. Usually in the case of the leg the disease does not extend above the knee, although instances of implication of the thigh are by no means rare; in the latter case folds and sulci around the joints permit some degree of motion. The margin of the diseased patch may be rather abruptly defined, or it may pass gradually into sound skin.

When the scrotum is affected the tumour assumes, as it enlarges,

pyriform shape, the neck of the swelling being towards the pubes. The penile integuments, as a rule, are dragged down into the mass, so that the penis becomes buried at the upper part, the glans lying at the bottom of a long tunnel which opens half-way down, or even lower, on the anterior surface of the tumour. Sometimes the integuments of the penis are specially affected, and then they form a long projection like a ram's horn, springing, as it were, from the face of the mass. In all cases the testes are dragged down in consequence of the fibrous attachment they have to the bottom of the scrotum through the remains of the gubernaculum testis; consequently the cords are very much elongated. Frequently the testes carry large hydroceles; very often they are deformed or atrophied by pressure.

In the case of the legs a girth at the calf of from 20 to 24 inches, and in the case of the scrotum a weight of from one to two pounds up to 50, or 100 or even 200 pounds, may be attained. An average measurement for a leg in a state of elephantiasis would be 21 to 22 inches; an average weight for a scrotal tumour 10 to 30 pounds. The skin of the mammae, when this organ is attacked, may enlarge till the nipple hangs as low as the umbilicus or pubes; cases are on record in which the mamma reached the knee and weighed many pounds. Labia weighing seven or eight pounds have frequently been removed.

Circumscribed patches of elephantised integument are not uncommon. Corney and Daniels described such patches as frequent among the Fijians, in whom, when the skin over Scarpa's triangle is affected, they form massive pear-shaped tumours many pounds in weight.

On cutting into the affected tissues in elephantiasis the dermis and external layers of the subcutaneous areolar tissues are found dense, white, fibrous, and enormously thickened—perhaps attaining a thickness of from one to two inches—particularly in the scrotum. The deeper part of the superficial fascia is converted into a loose, yellowish, blubbery-looking dropsical tissue containing here and there fibrous bands and many large veins and lymphatics. The sheaths of the large vessels and nerves, and the muscular aponeuroses are thickened; the underlying bones may also be hypertrophied and rough. The lymphatic trunks are dilated, and their radicles varicose and thinned.

In all cases the lymphatic glands are enlarged, dense, and fibrous; and not the glands of the affected side only, but often those of the opposite limb also.

Ulcers sometimes form on the affected limbs, and in the larger scrotal tumours large abscesses and even gangrenous patches are not uncommon.

Apart from the risks attending secondary septic conditions arising from such mishaps, elephantiasis, though painful when inflamed, and cumbersome at all times, is not a disease involving much danger to life.

*Pathology of Elephantiasis.*—The pathology of elephantiasis is still obscure. Although there is sufficient evidence to connect it with *Microfilaria nocturna*, the exact way in which the parasite brings about



the lymph stasis, which pathologists agree to be the main factor in the disease, is still a matter of speculation.

The following are the principal grounds for incriminating the filaria. (a) The geographical ranges and the degrees of prevalence of elephantiasis and, so far as we know, *Microfilaria nocturna* correspond. (b) Elephantiasis is a disease essentially of the lymphatic system; the filaria, in its mature form, is essentially a parasite of the same system. (c) Elephantiasis frequently accompanies or supervenes on the elephantoid diseases. (d) The elephantoid diseases themselves diseases of the lymphatic system—are generally associated with a peculiar type of fever and inflammation, the same type of fever and inflammation is always a feature in the development of elephantiasis. (e) Seeing that elephantoid diseases have been proved to be caused by the filaria, it is reasonable to conclude that elephantiasis is brought about by the same parasite.

There are certain cases of lymph-scrotum and of varicose groin glands in which the contents of the lymphatic varix are clear and lymphous, and not, as is usually the case, chylous. Manifestly such contents come from leg or scrotum only, and are not, in such instances, a regurgitation from the intra-abdominal lymphatic system. Sometimes in these cases filaria embryos are found in the lymph from the varix although they cannot be found in the blood. The inference from this fact is that the lymph containing the parasite cannot reach the circulation, otherwise the filaria would be discoverable in the blood. On two occasions, in examining the lymph in such cases, large numbers of filaria ova, measuring  $\frac{1}{60}$ " by  $\frac{1}{100}$ ", were encountered. In this circumstance the explanation of the pathology, not only of the particular class of varix in which these ova occurred but also of elephantiasis, may possibly be found.

The filaria is normally viviparous. Its young, when born, are long outstretched animals possessing the power of independent movement, and to a certain extent of locomotion. Though long they are no broader than a red blood-corpuscle, and therefore can pass wherever red blood-corpuscles can pass. But the ova of the filaria are very much broader bodies, they are passive, and therefore incapable of contributing to their own passage through the vessels. The presence of ova in lymph proves that the process of parturition in the filaria from which these particles proceeded had been morbidly hurried, in other words, the contents of the parasite's uterus had been discharged before the intra-uterine development had been completed, before the spherical ovum had been converted into the elongated embryo. The effect of such an occurrence on the lymphatics in which the mature filaria lies may be imagined.

Under normal conditions the microfilarie proceeding from a parent worm traverse the lymphatic glands without difficulty, but should an injury to the female filaria—an event very likely to occur in so exposed a situation as the leg—cause her to abort—to empty her uterus prematurely—then, instead of the long, slender, sinuous, active embryo, the broad, passive, spherical ova from the upper end of the parasite's uterus will be launched into the lymph stream. These ova will be



carried to the nearest lymphatic gland, and, being too large to traverse the vessels, will plug the entire system of afferent vessels appertaining to this gland. Then the anastomosis will carry the arrested and diverted ova-bearing lymph-stream to the next gland. This gland will be plugged in turn; and so on until the entire lymphatic system connected directly or by anastomosis with the vessel in which the aborting filaria lies is completely cut off from the circulation. A slight blow, or wound, or septic inoculation would readily set up inflammation in such a congested area and elephantiasis will be established.

Objection has been raised to this hypothesis on the ground that micro-filariae are rarely found in the blood in elephantiasis. This objection is readily answered by the consideration that the very circumstances and mechanism by which the filariae bring about the disease prevent their embryos from appearing in the blood; these cannot traverse the occluded glands any more than the lymph can.

It is a curious and significant circumstance that in a country in which both elephantiasis and the filaria are extensively endemic, filariae are found very much more frequently in individuals who are not affected with elephantiasis than in persons who are so affected. Thus, in 88 blood-slides received from Cochin, 74 came from healthy individuals—in these 74 slides filariae were found in 20, or in about 1 in 3·7; 14 came from cases of elephantiasis, but in only 1 of these 14 slides were filariae found. These figures not only prove the great frequency of the filaria in countries in which elephantiasis is extensively endemic, but they are a powerful support to the opinions offered concerning the particular way in which the parasite brings about this disease. In such countries filariae are less likely to be found in those persons who are affected with elephantiasis than in those who are not, seeing that in the former the lymphatic system of a considerable part of the body is blocked. But in countries in which the filaria is still more prevalent—in which nearly every man and woman carries the parasite—even those affected with a moderate area of elephantiasis may have the microfilariae circulating in the blood. Thus, of 56 slides of night blood, from 56 cases of elephantiasis and elephantoid conditions, which Dr. Davies collected in Samoa, no fewer than 27 contained the filaria, many of them in great profusion.

Many other hypotheses of the causation of elephantiasis have been advanced from time to time, but none of them explain or, indeed, are compatible with all the facts now ascertained about this disease.

*Treatment of Filariasis.*—No means have been discovered of killing the filariae in the body, and as it is impossible, with rare exceptions, to localise them with sufficient precision, excision of the parent worms is usually out of the question. The only way to secure immunity from filarial disease in the endemic region is by a rational prophylaxis founded on our knowledge of the life-history of the parasite. The subjects of filarial infection should be made to sleep below mosquito-netting. In filaria countries every one should use mosquito-nets, and mosquitoes

should be suppressed as far as is practicable (cf. p. 285). Persons known to harbour filariæ ought to avoid blows and injuries of all kinds, and every circumstance which might cause the parent filariæ to abort, or which might cause rupture or set up lymphangitis in congested lymphatic areas.

The pathology of the various forms of filarial disease indicates their special treatment.

*Chyluria* is best treated on mechanical principles, effort being directed to lessen the pressure on the vessels of the leaking renal or vesical lymphatic varix. The recumbent position with raised pelvis should be maintained until the urine becomes clear and free from clot and albumin. All foods likely to increase the amount of chyle, such as fats and albuminoids, should for a time be avoided, and the amount of fluid restricted as much as possible. By following such a dietary the chylous appearance in the urine often disappears in a day or two. This does not mean cure, however, in every case; for if we inspect the urine carefully we can still, and for a longer or shorter time, see floating in it a lymphous clot, and on boiling find it loaded with albumin. So long as clot and albumin are present, the leak in the lymphatic varix is not healed, although the fatty matter, not being supplied to the chyle, may not be present. A single tumblerful of milk will at once give ocular proof of the patency or closure of the rupture in the varix. Not until clot and albumin have entirely disappeared, and the milk test gives a negative result, should the patient be allowed to quit the recumbent position.

It is well to give a saline aperient from time to time. Many drugs have been recommended, including benzoic acid and the benzoates, gallic acid, the salts of iron, glycerin, mangrove bark, chromic acid, thymol, salicylate of soda, and so on, but it cannot be said that benefit has certainly accrued from any of them. In judging of the value of a remedy in this disease it must always be borne in mind that every now and again chyluria ceases spontaneously; the drug which was being taken when the chyluria so ceased is apt to be credited with the cure.

*Varicose inguinal glands* ought to be left alone or gently supported by a well-adjusted bandage. If they are so painful and so tense that the patient is thereby disqualified from making a living, the question of their excision might be entertained. But the surgeon must not forget that these dilated lymphatics are part of a physiologically necessary varix. Although their excision has been followed sometimes by chyluria and also by elephantiasis, in not a few instances the operation has been productive of benefit which appeared to be permanent (Maitland). In a case operated on by Mr. Johnson Smith, the lymphatics of the right spermatic cord subsequently became enormously dilated and caused much pain and inconvenience. Mr. Godlee has attempted, by introducing one of the dilated lymphatics into a convenient vein, to short-circuit the course of the lymph to the venous system, and thereby reduce the pressure in the varix. The result was not completely successful owing to the tenuity and delicacy of the lymphatic walls.

*Lymph-scrotum*.—The same remarks apply to this as to the preceding case. When passing into confirmed elephantiasis a lymph-scrotum ought to be excised.

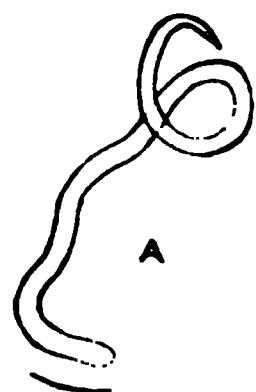
*Chylocele* may be tapped and injected or incised.

*Elephantiasis of the scrotum* should be amputated, the penis and testes being retained.

*Elephantiasis of the leg* is best treated by rest, elevation, massage, and elastic bandaging. If of recent formation, and the patient sound in constitution, and neither malarious, anæmic, nor scorbutic, a mild mercurial course may be beneficial. During acute attacks pricking the distended limb so as to provide an escape for the effusion, and dressing the parts antiseptically, gives great relief, and may tend to delay the progress of the swelling. Pain and fever are to be treated on general principles.

xiii. *Filaria magalhaesi* R. Blanchard 1895.—(Synonyms: *Filaria bancrofti* von Linstow 1892, *Filaria bancrofti* P. S. de Magalhães 1892 *nec* Cobbold 1877.)—In 1892 Professor Magalhães, of Rio de Janeiro, published a careful description of two sexually mature filariæ which were found in a clot of blood said to have come from the left ventricle of the heart of a child. The disease of which the patient died is not stated. The female measured 155 mm. in length by 0·6 to 0·8 mm. in breadth, the male 83 mm. in length by 0·28 to 0·4 mm. in greatest breadth. Both were white, opalescent, and delicately marked by transverse striæ. In both the œsophagus terminated in a bulb, the intestine commencing in a dilatation; and in both the head was club-shaped, and the mouth terminal, round, simple, and without papillæ. In the female the vulva was placed 2·56 mm. from the mouth, the uterus was double, and the anus opened 0·13 mm. from the tip of the rounded tail. The male was provided with two spicules projecting from the cloaca, 0·11 mm. from the tip of the rounded tail, which was further provided with four pre-anal and three post-anal pairs of papillæ. We have no description of the embryos, which, it is to be presumed, must have circulated in the blood.

xiv. *Filaria demarquayi*<sup>1</sup> Manson 1895.—The geographical range of this parasite has not yet been accurately determined, but we know it occurs in certain of the West Indian Islands—St. Vincent, Dominica, Trinidad, and St. Lucia, and in Demerara. The same or a similar



x300

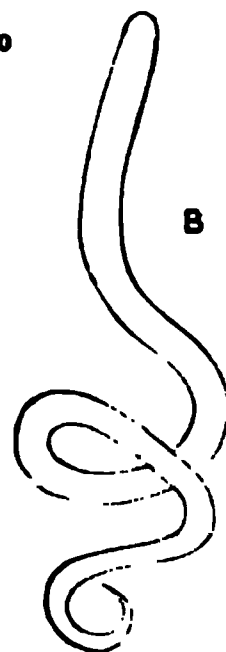


FIG. 204.—A, *F. demarquayi*. B, *F. nocturna* (x 300). Drawn from slides prepared in the same way.

<sup>1</sup> This blood-worm, *Filaria demarquayi*, was named, at Professor Blanchard's suggestion, after Demarquay, the discoverer of *Microfilaria nocturna*, and therefore the pioneer of this important branch of pathology. Demarquay was a native of the West Indies; there is, therefore, a certain appropriateness in calling this West Indian parasite after him, as well as being a recognition of scientific services too long overlooked even by his own nation.—P. M.

parasite has been seen in blood from New Guinea and from the West Coast of Africa. In the West Indian Islands it is confined to very circumscribed districts, but in Demerara a large proportion of the native Indians throughout the back country are affected, and in them *Microfilaria demarquayi* is almost invariable in association with *Microfilaria perstans*. According to Low it is a parasite of jungly districts. The intermediary host has not yet been discovered. The microfilaria is characterised by its minute dimensions, sharp tail, absence of a sheath, and by its very active movements and capacity for elongation and contraction. A complete specimen of the adult male has not been found; the female occurs in the connective tissue at the root of the mesentery. It measures 65-80 mm. in length by 0.21-0.25 mm. in breadth. The head is simple, unarmed, there is no œsophageal constriction. The anus is subterminal, opening on a small papilla 0.25 mm. from the posterior extremity. The genital pore opens 0.6 mm. from the mouth. The embryo shews no periodicity. The intermediary host is not known, though there is some reason for suspecting *Stegomyia fasciata*.

Hitherto *F. demarquayi* has not been shewn to be pathogenetic. *Filaria ozzardi* Manson 1897.—This form has been described as a distinct species, but it is now regarded as specifically identical with *F. demarquayi*.

xv. *Filaria volvulus* R. Leuckart 1893.—This worm, known only in the adult state, is found in subcutaneous tumours in men on the Gold Coast, Dahomey, and Sierra Leone. The male measures 30 to 35 by 0.144 cm. The cuticle is thick and striated; the tail is recurved. There seem to be a pre-anal and a post-anal pair of papillæ, and two lateral pairs and two unequal spicules. The female is 60 to 70 cm. long and the truncated tail is recurved. The embryos abound in the fluids of the tumour, they measure 0.25 by 0.005 or 0.006 mm. They have not yet been recognised in the blood. The worms can live in the tumours for many years.

xvi. *Filaria powelli* Powell 1903.—This is only known in the microfilarian state, and requires reinvestigation. It was found in the blood of a Mohammedan policeman in Bombay. The microfilaria has a sheath, is 0.13 mm. long, and uniformly 0.005 mm. thick. It was only found at night.

### Family VI.—Angiostomidæ

Heterogeneous Forms.—This family, like the preceding, also includes only one genus parasitic in man. The various species are heterogamous, each species including a free, bisexual, and rhabditic form and a parasitic, filaria-like, and hermaphrodite form.

*Strongyloides stercoralis* Bavay 1876.—(Synonyms: *Anquillula intestinalis* et *stercoralis* Bavay 1877, *Leptodera intestinalis* et *stercoralis* Cobbold, *Pseudorhabditis stercoralis* Perroncito 1881, *Rhabdonema strongyloides* Leuckart 1883, *Strongyloides intestinalis* Grassi 1883, *Rhabdonema*

*intestinale* Blanchard 1886.)— This parasite, discovered by Normand in 1876 in cases of chronic intestinal flux from Cochin China, has since been found in many parts of the world—in Brazil, West Indies, Egypt, India, Ceylon, China, Indo-China, the United States, the Philippines, Hawaiian Islands, Africa, Italy, Germany, etc. It is very often found in association with *A. duodenale*, and it is probable that the geographical range as well as the biological requirements of these two parasites are closely similar.

The mature rhabdonema lives in the intestinal mucus of the duodenum and upper part of the jejunum; rarely in the stomach or ileum. It is a very minute and, proportionately, very long parasite—2·2 by 0·034 mm. It is readily distinguishable under the microscope from all other intestinal parasites by its size and proportions, and by the five or six ellipsoidal eggs (0·05 to 0·058 by 0·03 to 0·034 mm.) lying in a string about the centre of its body and in close relation to the position of the vulva. No male form has been found in this stage. From analogy with *Rhabdonema*



FIG. 205.—Embryo *Strongyloides stercoralis* in faeces. After Golgi and Monti.



FIG. 206.—Egg of *Strongyloides stercoralis* (x about 400). Colourless. From LUNDA.

*nigrovenosum* of the frog Leuckart regarded these forms as hermaphrodite, but other observers look upon them as parthenogenetic females. They bore into the mucous membrane of the alimentary canal, often into Lieberkühn's glands. When the ova have passed into the chyme the embryo (Fig. 205) develops so rapidly that before the faeces leave the intestine the shell of the egg has been ruptured and the embryo is swimming about very actively in the fluid faeces. These embryos have pointed tails, rounded heads, and measure 0·2 or 0·3 by 0·013 mm. They are further distinguished by the double oesophageal bulb, the posterior bulb of which carries three teeth. Unlike what occurs in the case of *A. duodenale*, owing to the rapid development of the embryo and its early escape from the ovum, ova are rarely found in the stools, unless it be during the action of a powerful cathartic. When they do occur in the stools, being usually in strings of three or four, they are not likely to be confounded with the ova of any other parasite.

The future of the embryos after they leave the human body depends on several circumstances. First, unless they get access to non-putrefying fluid they soon die; the faeces containing them, therefore, must mix freely with water. Second, if the temperature be low the embryo rhabdonema develops into a filariform larva which, when

swallowed by man, or when it has bored through his skin and made its way to the intestine, quickly assumes the parasitic form already described. Third, if the temperature be high the embryos develop into male (Fig. 207) (0·7 by 0·035 mm.) with a coiled tail, and female (Fig. 208) (1·0 by 0·05 mm.) mature rhabditic worms. Their eggs, which number only 30 to 40, measure 0·07 by 0·045 mm. In due time these rhabditic

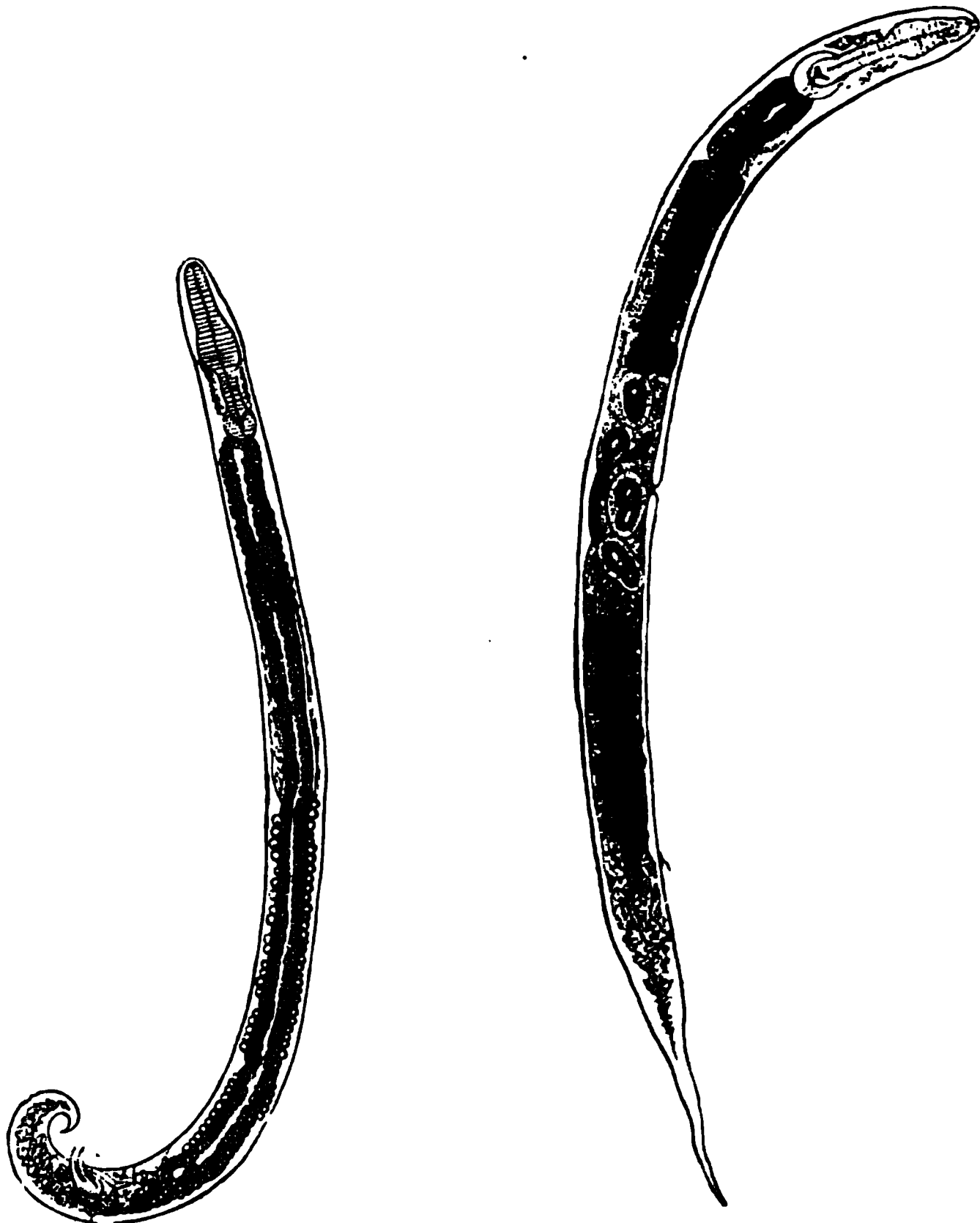


FIG. 207. —*Strongyloides stercoralis*, male. Golgi and Monti.

FIG. 208. —*Strongyloides stercoralis*, female. Golgi and Monti.

forms produce embryos which assume the filariform type (Fig. 209) and, on being transferred to man, become *Rhabdonema intestinale*. These free mature rhabditic forms are what were formerly known as *Anguillula stercoralis*. They were found in the fæces at post-mortem examinations, and also in the fæces after discharge; for a long time their true relationship to the *R. intestinale* was not understood. Grassi has shewn that the second or free generation may be suppressed and that the first larvæ may grow up



into the parasitic form directly. This may account for the great severity of the infection in some cases.

At one time this parasite was supposed to be the cause of the diarrhoea so common in Cochin China. This is no longer believed, and most pathologists regard the presence of the worm in these cases as more or less accidental—favoured no doubt by the catarrhal condition of the intestinal mucous membrane, but certainly not causing it.

The eosinophil cells of the blood are usually increased in number in this infection (up to 14 per cent); in some cases an increase in the number of lymphocytes has been noted, but no cases of anæmia or general leucocytosis have been traced to the presence of this parasite.

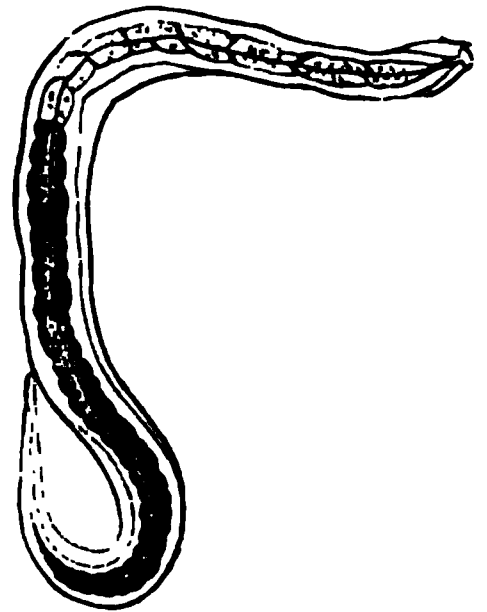


FIG. 209.—Filariform embryo of *Strongyloides stercoralis*. Golgi and Monti.

The larvæ of the free forms make their way into the body of the host, like the larval *Ankylostomus*, in two ways. Either (i.) passively in drinking-water or in food such as salads, or (ii.) actively by boring through the skin whence they reach the alimentary canal through the same channels as do the *Ankylostoma* larvæ.

*Treatment.*—*R. intestinule* is difficult to expel. Sonsino says he got good results from a long course of small doses of thymol and liquor ferri perchloridi. The ordinary anthelmintics are ineffective against this parasite. Prevention must take the direction of a pure water-supply and the avoidance of uncooked vegetables and fouling of the skin by fæcally contaminated soil. There is some evidence that the desiccated filariform embryos may gain access to the alimentary canal in the shape of wind-borne dust.

#### Family VII.—Gnathostomidæ

The anterior part of the body or the whole body covered by minute branching spines. Usually found in the alimentary canal of mammals. Only one genus.

**Gnathostoma siamense** (Levinsen) 1889.—(Synonym: *Cheiracanthus siamensis* Lev. 1889.)—The female, measuring 9 by 1 mm., alone is known. Around the head are eight rings of spines and the other spines cover only the anterior third of the body. The first specimens came from the breast of a young Siamese where a tumour had formed. The tumour disappeared and was succeeded by bean-like swellings in the skin; from one of these the worm came out. Two or three other cases have since been observed.

#### CLASS II.—ACANTHOCEPHALA

This is a small group with few genera, usually associated with the Nematoda and the Nematomorpha (Gordian worms) to form the group Nemathelminthes.

The Acanthocephala vary from 65 cm. in the female *Gigantiocephalus*

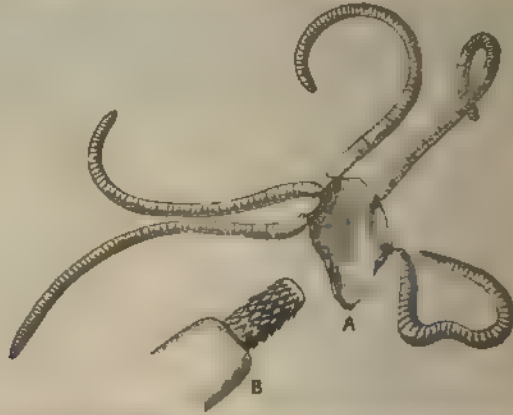


FIG. 210.—A, Five specimens of *Echinorhynchus acris* Rud attached to a piece of intestine (x 100). B, the proboscis of one still more highly magnified.

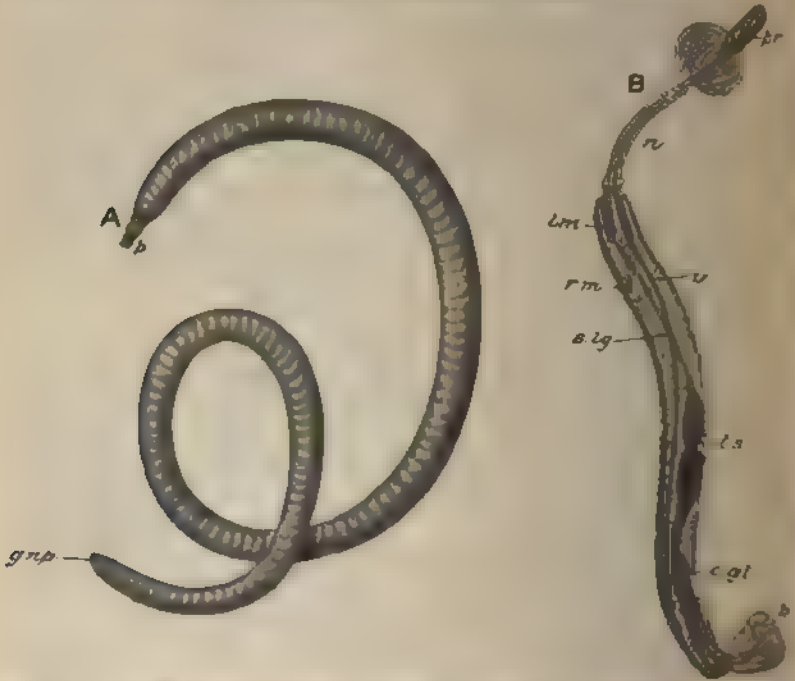


FIG. 211.—A, A female *Gigantiocephalus* found from a frog (x 100). B, A female *Gigantiocephalus* found from a frog (x 100). br, brain; rv, rectum; lm, lateral muscle; rm, rectal muscle; v, vagina; sig, sigmoid; ls, lateral sac; cgl, caecal gland; b, body.

gigas to quite small species a few millimetres in length. They are parasitic in the alimentary canal of vertebrates, usually in those which

live near water, for the larval stage is usually passed in a crustacean or in water-insects. There is no alimentary canal or mouth, and the animals live by absorbing through their general body-wall the nutritive fluids in which they are bathed. The anterior end of the body is called the proboscis, and is surrounded by rings of hooks which serve to fix the parasite in the walls of the alimentary canal. The lumen of the proboscis is cut off from that of the body by a septum, and to some extent the proboscis can be retracted into the body. The skin is smooth and whitish. The animals usually have a plump appearance.

The following three species have been described in man, but with little detail and some uncertainty:—

i. *Gigantorhynchus gigas* (Goeze) 1782.—(Synonym: *Tenia hirudinacea* Pallas 1781.)—The elongated body tapers posteriorly. The proboscis is almost spherical, with five or six rows of hooks. The male is 10-15 cm. in length, and the female may be three times this, or even more, in length. The three shelled eggs are 0·08-0·1 long. The normal host of *G. gigas* is the pig, and they live in his small intestine. The eggs leave the body and arrive in the grubs of the beetle *Melolontha vulgaris* and *Cetonia aurata*, and probably in America of *Lechnosterna arcuata*. It is of course only an accidental parasite in man, but, according to Braun, Lindemann states that it is not rare among the peasants of Southern Russia, and Leuckart admits a few cases.

ii. *Echinorhynchus hominis* Lambl 1859.—A boy who had died of leukaemia harboured an *Echinorhynchus*, to which Lambl gave the name *E. hominis*. The worm was 5·6 mm. long, and bore twelve rows of hooks in its proboscis.

iii. *Echinorhynchus moniliformis* Bremser 1819. The adult of this species is normally parasitic in field-mice, marmots, rats, etc., and the larva lives in a beetle *Blaps mucronata*. Grunni and Calandruccio have shewn that it will live in man if artificially introduced.

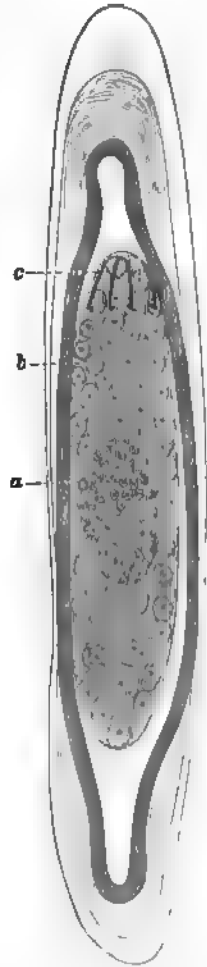


FIG. 212.—An egg of *Echinorhynchus aeneus* Stud. surrounded by three eggshells. Highly magnified. The egg has segmented, and the cells are differentiated into a, the entoblast, and b, the retoblast; c, spines. From Hamann.

#### PENTASTOMIDA

This group of animals occupies an isolated position in the animal kingdom. Most authorities regard them as aberrant Arachnids, but the

connexion, if it exists, is a remote one. It includes two genera with some score of species, all of them parasitic. The adults occur as a rule in the nasal passages and the spaces connected with them, and in the lungs of the carnivora, ophidia, and crocodilia and flesh-eating vertebrates generally. The larvæ occur either free in the body-cavity or encapsuled in the walls of the alimentary canal, the mesentery, the liver, spleen, or abdominal muscles; in fact in some position not far removed from the alimentary canal from which they have migrated. Both adults and larvæ sometimes shift their position, and the active migration of the latter may cause fatal results.

The Pentastomida are white, rather tough, worm-like animals, with a series of constrictions and rings which have no true segmental value. The head may or may not be separated from the body by a neck, it bears the median mouth, and is flanked on both sides by a pair of stout hooks. The anus is terminal. Pentastomids are bisexual, the males being, as a rule, smaller and less numerous than the females. The uterus opens ventrally a little in front of the anus, and the number of ova is very great. The male genital opening is also ventral and a little way

behind the mouth. The ova pass out of the body of the host with the mucous secretion discharged from the nose, or in some cases they may possibly pass through the alimentary canal; at any rate they reach the ground with its vegetation. Here they somehow get into the body of the second host, a fish, a bird, a mammal such as a mouse, in fact some animal likely to be eaten by the carnivorous host of the adult.

Only two or three species occur in man who is only sporadically their host.

1. *Linguatula rhinaria* (Pilger).—(Synonyms: *Tenia rhinaria* Pilger 1802, *Polydora tenioides* Rud. 1810, *Linguatula tenioides* Lam. 1816, *Pentastoma tenioides* Rud. 1819.)—The adult lives in the nasal cavities of dogs, wolves, horses, and rarely man. A case is recorded by Laudon of a soldier in the Franco-Prussian war who suffered for seven years from the presence of one of these creatures in his nose. It was finally expelled by a sneeze in 1878, and the nose-bleeding and inflammation at once subsided.

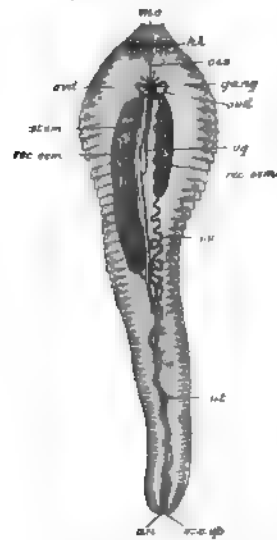


FIG. 213. — *Linguatula rhinaria*, young female. an, anus; gang, ganglion; aa, hooks; mo, mouth; oes, oesophagus; ov, ovary; ovid, oviduct; rec. ut, receptaculum seminis; rec. ap, sexual aperture; stom, stomach; ut, uterus. After Lauekart.

The larva of *L. rhinaria*, which often goes under the name of *Porocephalus* (*Pentastoma*) *denticulatus*, is much more common. Zenker, who first recognised it as a human parasite, found it nine times in one hundred and sixty-eight post-mortems; Heschl found it twice in twenty autopsies, and there are many other cases on record.

2. *Porocephalus constrictus* (v. Sieb.) (a larval form).—(Synonyms: *Nematoideum hominis* Diesing 1851, *Pentastomum constrictum* v. Siebold 1852, *Porocephalus constrictus* Stiles 1903.)—The parentage of this larva is doubtful. Shipley considered it to be *P. armillatus* Wyman, which lives in the lungs of African pythons (*Python sebai*, and *P. molurus*) and also in the lion. Neumann regards it as the larva of *P. moniliformis* Diesing, which also lives in African pythons, whilst Looss thinks that these two species are identical.

The larva has twenty large and distinct rings, and just behind the head a region of minute and undetermined annuli. It is found curled up and encysted in the mesentery and connective tissue of the giraffe *Proteles cristatus*, *Cynocephalus marmon*, *Cercopithecus albogularis*, and of *Homo sapiens* in Africa. Occasionally it wanders freely in the alimentary canal and in the body-cavity. Aitken, whose work refers to the soldiers of the African British colonies, met it also in the liver and lungs, and he states that it causes death.

#### HIRUDINEA (LEECHES)

The leeches are a group of segmented worms descended, in all probability, from the Chætopoda or true worms. They are divided into two groups: (i.) the Gnathobdellidæ which are armed with three biting jaws; (ii.) the Rhynchobdellidæ which are provided with a protrusible proboscis. In the grown-up condition they suck blood, preferably from warm-blooded animals, and when biting they secrete, from certain glands in the pharynx, a secretion which prevents the blood coagulating, and consequently the blood often flows after the leech has ceased biting.

But two of the identified species are really harmful to man, and they both belong to the Gnathobdellidæ.

(i) *Limnatis nilotica* (Sav.). — (Synonyms: *Bdella nilotica* Sav. *Limnatis nilotica* Moq.-Tand., *Hæmopsis vorax* Moq.-Tand. 1826, *Hæmopsis sanguisuga* Moq.-Tand. 1846, *Sanguisuga ægyptiaca* Moq.-Tand.)—The length is 8-10 cm. and the anterior end is the more pointed. The dorsal surface is brownish-green, with six longitudinal stripes, the ventral surface is dark. This leech lives in fresh water, and is found from the Azores and Canaries along the northern edge of Africa into Syria, Armenia, and Turkestan. It caused great trouble to the members of the French Army when Napoleon invaded Egypt. It passes into man and into domestic animals with the drinking-water. It remains in the stomach for a time, and then begins to wander. It crawls into the œsophagus, the throat, the nasal cavities, and sometimes into the trachea. It has also been found in the vagina and in the conjunctiva, but it seems unable to bite through the outer skin. It causes various symptoms according to the position it takes up. Headaches, epistaxis, difficulties in respiration, the expulsion of mucus mixed with blood, a tendency to vomit, and if of long duration a certain degree of emaciation. The leeches can be expelled by spraying with salt solution.

*Hæmadipsa ceylonica* Moq.-Tand. is perhaps the best represent-

ative of a genus of land leeches which causes great trouble to travellers. *H. ceylonica* extends from India and Ceylon through Burma, Cochin China, Formosa to Japan, the Philippines and Sunda islands. Other species occur in South America, New Guinea, and Australia. These leeches live on damp earth, but they ascend plants and shrubs to obtain a better outlook for the arrival of a victim. Landon, in his *Notes* (London, 1905), writing at Sikkim, states: "The game here is very scanty: the reason is not uninteresting. For dormant or active, visible or invisible, the curse of Sikkim waits for its warm-blooded visitor. The leeches of these lovely valleys have been described again and again by travellers. Unfortunately the description, however true in every particular, has, as a rule, but wrecked the reputation of the chronicler. Englishmen cannot understand these pests of the mountain side, which appear in March and exist, like black threads fringing every leaf, till September kills them in myriad millions . . . to remove them a bowl of warm milk at the cow's nose, a little slip-knot, and a quick hand are all that is required. Fourteen or fifteen successively have been thus taken from the nostrils of one unfortunate heifer." Travellers relate that in stepping into the forest they can hear the leaves rustling with the movements of these eager creatures, craning out towards their prey. They can insinuate their bodies through the minutest chinks; tightly-fitting clothes and leather gaiters prove inadequate protection. Their bite is quite painless. When they are fully fed, a process which takes some time, they drop off, and they can be made to loose their hold by the application of a solution of salt or weak acid. Attempts to pull them off should be avoided, as parts of the biting apparatus are then frequently left in the wound and cause inflammation. As a rule the bites, which are so painless that the presence of the leech is often only observed by noticing a trickling of the blood, heal well, but at times they become infected with bacteria and cause much trouble. When a large number attack a man great weakness ensues from the loss of blood, and people attacked in their sleep by a numerous host of these leeches have succumbed to their united efforts.

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A. E. SHIPLEY.

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E. G. F.

## HYDATID DISEASE

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**Historical.**—The history of the growth of our knowledge concerning hydatids, as understood in this article, is intimately associated with that of bladder-worms in general; especially in all that relates to their biological aspects.

There is little doubt that as a pathological phenomenon hydatids were recognised by Hippocrates. He writes: "When the liver is filled with water and bursts into the epiploon, in this case the belly is filled with water and the patient dies" (16). Aretæus,<sup>1</sup> who flourished about the middle of the second century of the Christian era, still more specifically indicates the disease as a form of dropsy due to "small and numerous bladders full of fluid," and he goes on to speak of the blocking of the cannula by the bladders in paracentesis. They are again mentioned by Galen in his comments on the above-quoted aphorism of Hippocrates, which, in his opinion, refers to hydatids.

Evident allusions to hydatids and other bladder-worms occur in the works of the medical writers of the sixteenth and seventeenth centuries without, however, any recognition of their animal nature. The term, moreover, is frequently applied to encysted accumulations of watery fluid of many kinds. It was not until 1684 that the animal nature of bladder-worms appears to have suggested itself to Redi; and in 1685 and 1691 respectively Hartmann and Tyson reached similar conclusions apparently independently of one another.

Pallas studied the subject of bladder-worms between 1760 and 1767, and clearly recognised a relationship with tænia. According to him all bladder-worms were forms of tapeworms, to which he gave the name *Tænia hydatigena*. He also recognised that the livers of sheep and cattle contained bladders having characters different from those of other vesicular worms; and he drew important distinctions between adherent

<sup>1</sup> The passage (1) deserves to be quoted in full, as the reference to abdominal hydatids and to contingencies that may arise is so precise. "This other form of dropsy is known: small and numerous bladders are contained in the place where ascites is found; but they also float in a copious fluid, of which this is a proof; for if you perforate the abdomen so as to evacuate the fluid, after a small discharge of the fluid a bladder within will block up the passage, but if you push the instrument further in, the discharge will be renewed. This, then, is not a mild character, for there is no ready passage by which the bladders might escape. It is said, however, that in certain cases such bladders have come out by the bowels."

serous cysts and non-adherent hydatids, remarking that "it is probable that the latter sometimes observed in the human body are either a species of vesicular tænia or of those *Hydatides singulares* that I have observed and described in the liver and lungs of sheep, which ought certainly to be ascribed to a living creature." He observed, without recognising their nature, the echinococcus heads in the *Hydatides singulares*; and, moreover, was the first to suggest the experimental administration of eggs of tænia to animals. His observations were confirmed by Goeze in 1782, who further indicated the existence of the general membrane lining the vesicles, and considered the echinococcus heads to be tæniæ.

More or less clearly expressed references to hydatids in the human subject occur towards the close of the eighteenth and beginning of the nineteenth centuries; and in 1821 such a case is specifically described by Bremser, and in the following year by Rendtorff.

Laennec, meanwhile, having failed to find in the hydatids of man the echinococcus heads with which he was familiar in the hydatids of domestic animals, nevertheless recognised their animal nature, and founded for them a separate genus which he called *Acephalocystis*.

So far the exact relationship of the bladder forms to the tænia head had not been made apparent: but a great impetus to our knowledge was given in 1842 by the application of Steenstrup's theory of the alternation of generations to the cystic worms. In the light of this discovery Dujardin, von Siebold, and van Beneden investigated the subject without, however, fully appreciating the true characters and relationships of the bladder forms.

Our systematic knowledge of this subject may be said to date from the feeding experiments of Küchenmeister in 1851. By this means it was clearly demonstrated that certain bladder-worms are the larval stages of certain tapeworms. In the following year, by the successful breeding, in the dog, of *Tænia echinococcus* from echinococcus cysts of the domestic animals, a similar relationship was proved to exist between these two forms by von Siebold and, shortly afterwards, by Küchenmeister. These experiments were repeated by Haubner, Leuckart, and Nettleship. With human echinococci the experiment failed in the hands of Küchenmeister and Zenker, but a measure of success attended Naunyn in Berlin and Krabbe in Iceland. More recently similar successful experiments with human echinococcus cysts were carried out by Thomas in Adelaide, South Australia.

The converse experiment of administering the ova of *Tænia echinococcus* to animals was carried out by Leuckart in conjunction with Haubner in the case of the lamb, sheep, and goat, without definite results, though it is probable that even in these experiments migration of the embryos into the viscera did take place; in the case of the pig, however, the experiments were eminently successful, and served as the basis of much of our knowledge concerning these parasites. R. Leuckart has exhaustively treated the whole subject of human parasites in his work *Die Parasiten des Menschen*, partially (1886) translated into



English by Hoyle a work which is essential to every student of helminthology.

Largely through the labours of the investigators whose names have been specially mentioned, as well as through those of Lavois, Huxley, Wagener, Vuchow, Rasmussen, Davano, Cobbold, Busk and others, the views have been established which will guide us in describing the anatomy, systematic position, development, and life-history of these parasites.

Of the radical treatment of hydatids, to be advocated in this article, the credit belongs to Lindemann, who appears to have first operated in this way in 1871; though no account of the operation seems to have been published for some years subsequently. This procedure has for some years been persistently advocated by various Australian surgeons, and amongst its earliest advocates must be mentioned the names of the late Drs. Gardner and Thomas; it is now generally adopted throughout the hospitals of Australasia.<sup>1</sup>

**Biology.**—Many of the internal parasites which take up their abode in the body of man are due to involuntary importations of organisms from the domestic animals. Amongst these the dog is the immediate source of those generally known as hydatids. This term, sanctioned by long usage, is applied to the larval or bladder stage of *Taenia echinococcus*, one of several parasites which are found within the alimentary canal of the different varieties of the domestic dog and of one or two allied species.

There are other parasites which exhibit a bladder phase of existence, such as *cysticercus* and *coenurus*, but general custom, in English-speaking countries at any rate, is inclined to restrict the term hydatid to the vesicular organism derived from the ovum of *Taenia echinococcus*, and it would be well that it should be exclusively so restricted. The name *Echinococcus* (ἐχίνος, a hedgehog; κόκκος, a berry introduced by Rudolphi in 1801), or *Echinococcus* disease, which is frequently used, especially by foreign writers, has undoubtedly the advantage of indicating the zoological relationship with the mature organism, but it is not always easy, and we think in this case not desirable, to dislodge a name that is not only well established and well understood, but also expressive of a chief physical characteristic. Moreover, the name *Echinococcus* is not always used in the same signification, being by some applied to the characteristic bladder itself inclusive of its contents, and by others restricted to those structures that will afterwards be described as scolices or *echinococcus* heads.

*Description of the Adult Tapeworm, Taenia echinococcus v. Siebold* (Figs. 214-217).—*Definition*.—A tapeworm of comparatively small size with usually four joints, but occasionally with three or five, of which the last, when

<sup>1</sup> See papers and discussions on 'Hydatid Disease,' *Transactions of the Australasian Medical Congress at Australasia*, 2nd and 3rd sessions. For a good bibliography of all that relates to the biology of the Cestode worms, see G. Rolleston's *Papers on Tropical Life*, 2nd edition, 1888, edited by Jackson. The manual of Cobbold and a monograph of Neisser also contain many bibliographical references to hydatid disease. Historical references are to be found in the treatises of Kuchenmeister and Davano.



mature, exceeds all the rest of the body in size. The total length is but a few millimetres, at most five. The small hooks have stout root-processes, and are seated on a somewhat swollen rostellum. Their number usually amounts to some thirty or forty (Leuckart).

To this definition we may add that the hooks, forming two series of from fourteen to twenty-five each, of which those of the inner row are

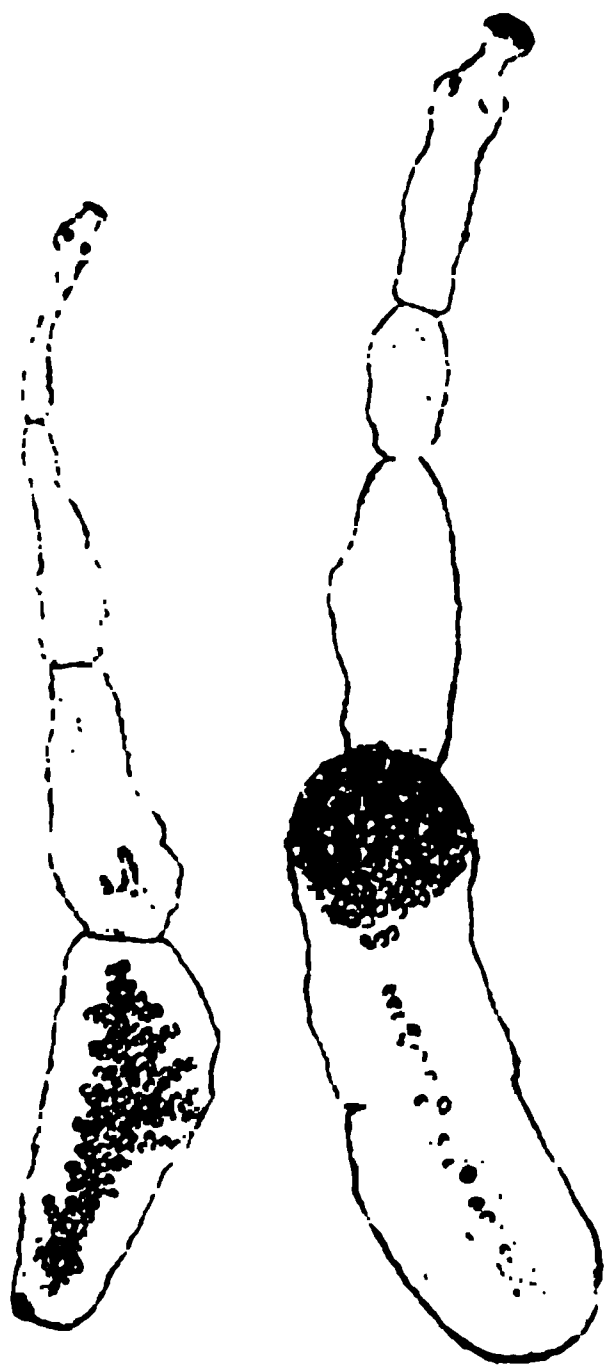


FIG. 214. — *Tænia echinococcus* showing usual disposition of ova in the terminal segment. From nature ( $\times 15$ ). The small figure to the left represents the life size of the *Tænia*.

FIG. 215. — *Tænia echinococcus* in which the ova are aggregated in the globular mass at the proximal end of the terminal segment. From nature ( $\times 20$ ).

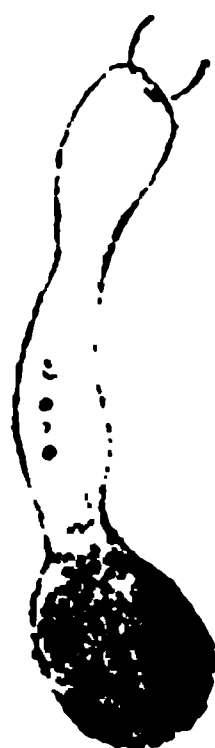


FIG. 216. — Terminal segment of *Tænia echinococcus* with ova aggregated at distal end. From nature ( $\times 20$ ).



FIG. 217. — Head of *Tænia echinococcus* showing circlets of hooks and two of the suckers. From nature ( $\times 175$ ).

the larger, are inserted into the base of the rostellum or proboscis-like anterior termination of the cephalic extremity, which in this species is somewhat pointed and prominent. By the musculature of this region the hooks are moved. They are further characterised by the relatively large size of their roots, but they vary in this respect according to the age of the worm (Fig. 218). They are often found deficient in number. Behind the circlets of hooks are four suckers radially disposed, and posterior to these the head elongates and narrows to form a neck. The next succeeding segment, or first proglottis, is imperfectly defined; it is short, and broader than the neck. The third segment, or second proglottis, is

longer and broader than the preceding, and in it the reproductive organs can already be distinguished. The fourth or terminal segment shows a

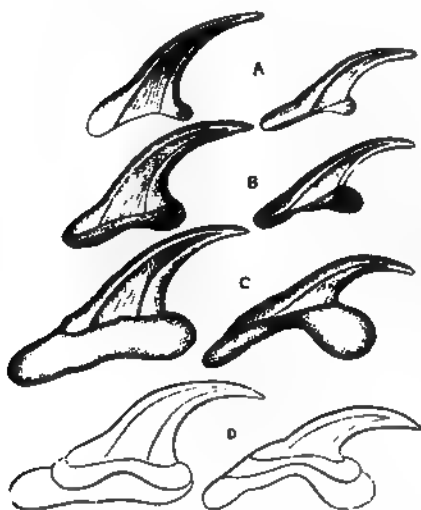


FIG. 218. Hooks of *Echinococcus* ( $\times 600$ ). From Leuckart. A, *Echinococcus echinococcus*; B, *T. echinococcus*, third week; C, *T. echinococcus*, adult; D, the outlines of the three forms drawn one within the other, to show their gradual changes.

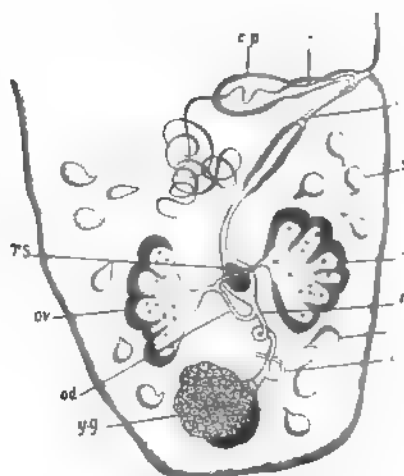


FIG. 219. — Reproductive organs of *T. echinococcus* - fertilisation ( $\times 80$ ). From Leuckart. cp, cirrus pouch; c, penis; o, ovary; od, oviduct; rs, receptaculum seminis; g, glands; ut, tube probably leading to uterus; fc, fertilising canal; v, vagina.

great increase in size, and contains, besides the completely developed reproductive organs (Fig. 219), eggs to a number estimated at 500 (Johns and Küchenmeister). Usually the eggs are distributed throughout the segment, but sometimes they are seen aggregated in a spherical mass either at the proximal or distal end (Figs. 214-216). The ova are covered with a resisting chitinous capsule and contain the already developed embryos or proscolices (oncospheres), which are armed with six spines<sup>1</sup> (Fig. 222).

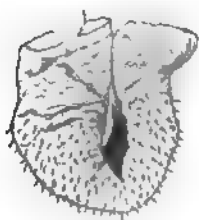


FIG. 220. Portion of duodenum of dog showing numerous *T. echinococci* attached to its mucous membrane. From nature ( $\times \frac{1}{2}$ ).

These worms are found, often in immense numbers, in the upper half of the small intestine of the dog (Fig. 220), where they lie buried amongst the villi with their terminal segments only exposed, and so closely resembling the villi that they are apt to escape notice. Under appropriate conditions they may be observed to exhibit active movements, in which the body may broaden or become extremely attenuated with corresponding shortening or lengthening. Their duration of life cannot be stated with precision.

<sup>1</sup> It will be well to distinguish these embryonic structures by this name, leaving the terms hooks and hooklets to be applied to the succeeding, permanent armature of the scolex and mature *Tenia*.

When the ripe terminal proglottides break off they are extruded with the faeces. Their soft tissues soon decay, and the liberated ova, enclosed and protected by their resistant chitinous envelopes, become scattered upon the soil or herbage, or get washed into collections of surface waters. Under these conditions the embryos, or possibly, in certain circumstances, the entire proglottides, may find their way into the alimentary canal of those domestic animals which are capable of serving as hosts for the subsequent phases of development, or it may be into that of man himself. If so ingested, the protecting chitinous envelope is softened and ruptured by the combined warmth and solvent action of the digestive fluids; and the embryo (Fig. 221), thus set free, begins an active life, boring, or rather pushing its way, by means of the movements of the hooks (Fig. 222), through the gastric or intestinal walls.<sup>1</sup> No one, we believe, has actually found the embryos of *Tænia echinococcus* in process of traversing these organs, but this has been observed in the case of those of *T. solium*, and they have been found by Leuckart in the portal vessels; it is also stated on the authority of Rohde that the ordinary form of echinococcus as well as the alveolar can develop within the lymph-vessels. The size of the free embryos is about three times that of a human red blood-corpuscle or about 0.02 mm.

The route taken by these active embryos is still largely a matter of conjecture, and the influences which may determine their distribution will be discussed elsewhere. From the frequency with which they are found in the liver, it is reasonable to suppose that the usual, or at any rate a frequent, course is into the portal system, in which, as just stated, they have been found. Possibly, however, they may push their way among the actual or potential spaces of the connective-tissue elements of the body; or, it may be, as just suggested, that they travel in the lymphatic spaces or vessels. Nevertheless the extreme rarity of hydatids in the lymphatic glands and closed lymphatic vessels is remarkable, and must be taken into account when we seek to explain the distribution of the bladders by a mere passive migration; so likewise must the conspicuous preference of the allied organism *Cysticercus cellulosæ*<sup>2</sup> (the vesicular product of *Tænia solium*) for the brain of man and to a less degree for his muscles, and of *Cænurus cerebralis* (the bladder stage of *Tænia cænurus*) for the brain of the sheep, where it produces the disease known



FIG. 221.—Hexacanth embryo of *Tænia echinococcus*, greatly magnified. After van Beneden.



FIG. 222.—A single spine of hexacanth embryo, greatly magnified. After van Beneden.

<sup>1</sup> The mechanism of these movements in the case of the similar hexacanth embryo of *Tænia dispar* is described by van Beneden.

<sup>2</sup> In 155 cases this parasite was found 117 times in the brain, 32 in the muscles, 9 in the heart, 3 in the lungs, and 5 in the subcutaneous tissue (Osler). For a detailed account of *Tænia solium* and *Cysticercus cellulosæ*, see p. 837.

as the "gid" or "staggers," as well as that of the echinococcus for the viscera, be taken to indicate something very like a selective affinity. Be this as it may, whatever the route or however impelled, the wandering embryo eventually comes to rest.

*Growth of the resting Embryo or Proscotex—Development of the Echinococcus Bladder.*—At the earliest stages at which these resting embryos have been with certainty observed—namely, by Leuckart in the pig four weeks after feeding with ripe proglottides—they form solid spherical bodies measuring 0·25 to 0·35 mm. in diameter, and bear a striking resemblance to a mammalian egg; that is to say, a thick, homogeneous, transparent and elastic cuticle or capsule (ectocyst, Huxley) encloses coarsely granular contents, as the zona pellucida encloses the granules of the yolk. In the course of subsequent development the proscotex increases in size, the external envelope becomes indistinctly laminated, and the contents more transparent, owing to a partial liquefaction. Fluid has, in fact, begun to accumulate in the interior, and the solid mass has become a vesicle with a gradually increasing quantity of fluid. With comparatively slight increase in the size of the vesicle an internal lining membrane appears upon the inner surface of the cuticle. This constitutes the germinal or parenchymatous layer (endocyst, Huxley). In this can be recognised an outer ill-defined layer of small cells and an inner containing larger cellular elements as well as muscle-fibres and calcareous corpuscles. The lamination of the cuticle becomes more marked, and remains always a conspicuous and characteristic feature, while its thickness increases with age. Meanwhile, even at this early stage, the presence of the growing organism excites changes in the tissues which harbour it; thus, by processes which will be discussed hereafter, an enveloping capsule of connective tissue is formed, bounding the parasite externally: this has been said to be lined internally by cellular elements and is the fibrous sac or adventitious capsule.

This structure, often improperly called ectocyst, though it is in no sense an organic part of the parasite, is nevertheless important to it as the immediate source of its nutritive supply; thus from a zoological point of view the relationship between host and parasite may be described as one of non-reciprocal symbiosis. Davaine and other authors maintain with good morphological reasons that the name cyst should be applied to this structure alone; but this name, by most writers, has been attached to the bladder-like organism itself; so that it is more convenient to retain this signification.

In the parasite itself a vascular system has not hitherto been recognised beyond doubt; moreover, the musculature which confers mobility upon some other larval forms is scanty. No trace of sexual organs exists. Amongst the cells of the parenchymatous layer are lenticular, laminated, calcareous particles, chiefly composed of carbonate of lime, which resemble in many respects corresponding bodies which form constant and characteristic elements in the cortical region of the body-parenchyma in the mature tapeworm, and indeed in the cestodes generally. Compared

with other forms in the bladder stage, that of *Tænia echinococcus* undergoes relatively slow growth, but, even when no more than 15 to 20 mm. in diameter (Leuckart), or, sometimes in our experience, considerably less, an important development may be already in progress which still further distinguishes this proscœlex from other varieties of bladder-worms: this is the formation of numerous heads or scolices.

The vesicular or bladder stage of tenia may (a) give rise to a single head; the resulting organism is then a cysticercus; (b) it may produce many heads, and the resulting organisms are termed conurus; or (c) there may be, as in echinococcus, many heads; these, however, are not produced directly from the germinal layer, as in the previous instances, but directly from special delicate sacs called brood-capsules,<sup>1</sup> which themselves originate from the proscœlex or bladder-worm.

*Development of Brood-capsules and Scolices* (Figs. 223, 224).—These structures arise as minute elevations in certain parts of the germinal layer by proliferation of its cells, which, according to Naunyn, bear

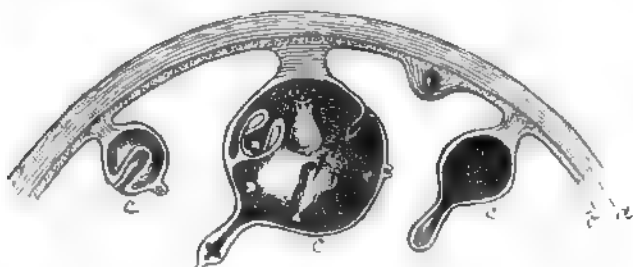


FIG. 223. Diagrammatic section of an *Echinococcus* bladder, with brood-capsules and scolices. From a wax model after Braun. a, cuticular or laminated layer; b, parenchymatous layer; c, brood-capsules with intra- and extra-verted scolices.

vibratile cilia that may persist even on the matured capsule. Within these elevations a small spheroidal cavity makes its appearance, gradually increases in size, and becomes lined internally with a delicate cuticular membrane; externally is a layer composed of cells. The wall of the brood-capsule thus exhibits two distinct layers, comparable to those of the mother bladder but inverted in relative position, which suggests that the brood-capsule represents an invagination of the former. Process and cavity grow to three or four times their original diameter, and, when fully grown, may attain the size of millet seed or about 1.5 mm. in diameter. Though muscular fibres have not been found in them, the brood-capsules exhibit active movements. They are extremely delicate and fragile, and thus it happens that unless special care be taken in the examination, or if the material be stale, they become ruptured, or may

<sup>1</sup> This statement, implying that the scolices are invariably derived from brood-capsules, though generally accepted, probably goes too far and may have to be reconsidered. We have had the opportunity of examining a specimen which shewed four heads sprouting directly from the germinal membrane of an exogenously developed daughter-cyst (human), of a size less than 1 mm. in diameter—smaller, in fact, than a brood-capsule—and possessing a relatively thick cuticle. Leuckart refers to similar observations.

even escape observation altogether. This has led to the view that the connexion between the heads and brood-capsules is only temporary, and that after separation the living scolices may float free in the fluid of the mother bladder. Leuckart, however, insists that all parts of the echinococcus—mother bladder, brood-capsules, and heads—are throughout life in direct continuity with each other, and we believe that he is correct.

A head (scolex) first appears as a discoidal thickening in the wall of the brood-capsule, which, relatively to the latter, grows into an externally situated club-shaped process perforated longitudinally by a canal-like continuation of the interior cavity of the brood-capsule. Though thus appearing as an external protrusion of the brood-capsule, it may at times be temporarily inverted, and indeed is frequently found so. At the bottom of the distal end of this hollow protrusion—namely, at that which is farthest from the point of its attachment—the distinctive elements of the scolex—the suckers and hooks<sup>1</sup>—are formed, the latter appearing as a thick fringe of prickles which subsequently all disappear except the foremost rows.

Histological differentiation progresses, and muscle-fibres, vessels, and calcareous particles become evident. At this stage the head as a whole becomes permanently inverted into the cavity of the brood-capsule: the contiguous walls of the hollow bud, and of the still hollow stalk by which it is attached, fuse; the scolex thus becomes a solid body attached to the interior of the brood-capsule by a slender muscular stalk. The anterior portion of the head which bears the suckers and hooks may, however, be invaginated within the remainder or hinder part, and may remain so for some time.

The views here adopted of the growth of the heads, often given in his own words, are those of Leuckart, who insists on the points that the scolices originate normally from the exterior of the brood-capsules and as hollow buds, in contradistinction to the views of other writers, who maintain that they arise from the interior or as solid bodies.

In this way, by successive development, heads of different ages to the number of ten, fifteen, or twenty may come to lie within one capsule. In the case of large bladders the included capsules may increase to the number of many thousands.

The young scolex, in the stage which it has now reached, has a spheroidal shape of about 0·18 mm. in diameter. As Leuckart remarks, it bears a striking resemblance to a vorticella with its ciliary circle retracted; and, as several heads are frequently seen in a group attached by their slender peduncles to a portion of the collapsed or ruptured brood-capsule, the further resemblance to a colony of these animals is equally remarkable. In the depression left by the invagination of the anterior extremity within the rest of the head are the suckers and the rings of hooklets, which can be seen shining through its translucent

<sup>1</sup> It will be understood that the original embryonic spines of the embryo or proscolia become dislocated and disappear at an early stage of development into the bladder form.



tissue (Fig. 215); under certain conditions—that is, by gentle warming of the natural fluid of the bladder—the heads may be made to exhibit movements, evaginate the retracted portion, and assume an extended form with a length of 0·3 mm. In this state they have the shape represented by Fig. 226, in which a partial constriction divides the head into an anterior and a posterior part. A small pit at the hinder end, which receives the attachment of the stalk, remains visible for some time after separation from the latter.

The hooklets have a general resemblance in form and arrangements to those of the head of the adult worm, differing only in the shorter and more slender shape of the roots (Fig. 218). In fact the description of the head of the adult worm may stand for that of the scolex in the stage of development which it has now reached. On reaching the



FIG. 224.—Later stage of development of brood-capsule showing external and internal scolexes ( $\times 40$ ). After Leuckart.



FIG. 225.—Scolex with invaginated anterior extremity ( $\times 100$ ). After Leuckart.



FIG. 226.—Scolex partially constricted ( $\times 100$ ). After Leuckart.

intestine of the dog, or other suitable host, the proglottides of the strobila or sexual worm are successively formed by a process of lengthening of its posterior end accompanied by transverse segmentation. The whole course of development, from the scolex condition to that of the adult worm, probably occupies from four to eight weeks.

*Formation of Daughter Bladders.*—The hydatid bladder, as we have traced it, consists of a single simple sac or mono-cyst, which may, however, attain an enormous size, bearing on its internal surface brood-capsules which contain scolices in varying number and stages of development. This form has received the name of *Echinococcus veterinorum*; but, in our experience in Australia it is not common in the domestic herbivora, while it is frequently found in man. There may, however, be a greater degree of complexity in its structure in which secondary and completely separated bladders may be formed; and these may either lie inside or outside the primary or mother cyst.

The varied forms of echinococcus bladders, recognised by the appli-

cation of the term *E. polymorphus* Diesing as one of the synonyms, based to the establishment of a number of names based, in some cases on views of specific distinctions that have proved to be mistaken, in others upon differences in their mode of proliferation. These synonyms have become very confusing, and it would be well if they were abolished, at least in medical treatises. Being convinced of the specific identity of all the ordinary forms of cystic hydatids, we propose to adopt one name, *Echinococcus hydatidosus* Leuckart, or its anglicised equivalent, for all the vesicular products, of whatsoever outward form, of the egg of *Trombidium echinococcus* von Siebold, using the qualifying term simply to designate single cysts uncomplicated by the presence of daughter bladders; while, if the latter have been formed, endogenous or exogenous will sufficiently explain the direction in which these have grown.<sup>1</sup> For the present the peculiar form *Echinococcus alveolaris* is left out of consideration (tab. p. 1029).

The former, or endogenous, type is that which, in our experience, occurs in man, and, we may add, in apes, with by far the greatest frequency, and almost to the exclusion of other hydatidose forms in the viscera – indeed, it was originally named *E. hominis* by Rudolphi. The secondary bladders arise (1) from vesicular transformation of echinococcus heads (scolices), which may be either floating free in the fluid of the parent bladder or still contained within brood-capsules; (2) from a similar transformation affecting the brood-capsules themselves; or (3) by a process, resting chiefly on the authority of Naunyn, which begins with a collapse of the original bladder from loss of some of its fluid, so that surfaces formerly separated come in contact and become adherent. The daughter bladders are formed by the metamorphosis of portions of the parenchymal layer which surround themselves by concentric chitinous lamellæ, and become hollow and filled with fluid. The process, as Leuckart remarks, bears a close resemblance to the method of exogenous budding to be next described. In any case separate secondary or daughter bladders are formed which lie within the parent cyst, and they correspond to them in structure and behaviour, and many likewise give rise to brood-capsules and scolices. By a resumption of the metamorphoses which have been described, the daughter bladders themselves may bud endogenously or exogenously, and thus produce a third or even a fourth generation within or without themselves, the whole brood being contained within the mother bladder.

The exogenous type, also occurring frequently, like the simple bladder, in the domestic animals and especially in the pig, is less

<sup>1</sup> Without intending to review, comprehensively, the whole synonymy of echinococcus bladders, we may here give the names that are most frequently in evidence in modern works. To the type of bladder which is either simple, or which gives rise to daughter bladders exogenously produced, the following names have been applied or proposed: *E. veterinarius* Rudolphi, *E. scolicipariens* Küchenmeister, *E. granulatus* Leuckart, *E. simplex* Leuckart, *E. cognatus* Kuhn, *E. cysticus fertilis* Braun. To the form producing internally developed daughter bladders: *E. hominis* Rudolphi, *E. altricariens* Küchenmeister, *E. hydatidosus* Leuckart, *E. endogenus* Kuhn.

common in man, though in him it is the form usually found in bone, while it occurs also in the brain and other extra-visceral localities.

In this form the secondary bladders arise from small granular masses which appear in the deeper layer of the cuticle of the mother cyst, though probably they are actually derived from the parenchymal layer. These assume a special cuticular covering of their own, and their central parts clear up and liquefy. With the continued centripetal formation of new layers in the cuticle of the mother bladder, and the rupture of its outer layers, these new formations gradually make their way externally, as completely separated sacs undergoing their subsequent development outside of the mother bladder, and usually close to it.

Sometimes the exogenous outgrowths may invaginate themselves into the parent cyst and appear as if they had been endogenously produced. If this process have been frequently repeated the original bladder may become packed with internal cysts really of exogenous origin, and the section of such a formation presents a labyrinthine appearance of septa and loculi, in short a multilocular arrangement.

Another special development of exogenous growth constitutes what we may term the "burrowing" type of hydatid, which has been sometimes confounded with the true alveolar form. This variety occurs extra-viscerally, is not met with in children, and fortunately is not common in adults. It is characterised by a more or less exuberant exogenous proliferation of cysts, which make their way along the fascial planes of the host and may thus travel to a considerable distance from the original nidus of the parasite. The conditions which give rise to this manner of growth may probably be thus explained. In those situations where, surrounded by a soft parenchymatous and vascular tissue, such, for instance, as the liver of a child, growth expansion is relatively easy and nutritive supply ample, the endogenous type obtains. Where, on the other hand, the storage capacity is limited and the resistance to expansion considerable, as in the confined spaces of cancellous bone, the symbiotic conditions are less favourable to the parasite, and it is driven into a struggle for existence. In these circumstances the parasite attempts to effect its growth by exogenous proliferation.

A similar response, under similar conditions, is seen in those cases of visceral hydatids of the endogenous type, where, from some cause or another, the adventitious capsule shrinks and acquires a leathery consistence



FIG. 227. Human Hydatid (Liver). The partially collapsed echinococcus bladder is seen within the adventitious capsule. Inside the former are two endogenously developed daughter-cysts, and on the outside are exogenous outgrowths. From nature.  $\times 2$ .

or even undergoes a considerable amount of calcification. These conditions also constitute a mechanical impediment both to active expansion from within and to osmosis from without, and the parasite may then fall into a sluggish or inactive phase in which it may remain quiescent, but alive, as long as the life of its host. Or, on the other hand, some cryptogenic pus infection, injury, surgical interference, or bile irruption may at any time kill it outright or initiate those suppurative processes which bring matters to a crisis.

During this inactive stage of indeterminate duration of a parasite a non-lethal injury may evoke a response in the form of exogenous proliferation that may even proceed to such an extent that it assumes the burrowing type. Probably such an event must be reckoned as one of those causes, observed elsewhere, which, it is suggested, may give rise to the frequently observed cases of multiple hydatids of the omentum and peritoneum.

It is thus that skeletal hydatids that have existed, perhaps for years, in a sluggish state giving rise to vague rheumatic-like pains may be quickened into an active life by a spontaneous fracture or by some inadequate, and often ill-advised, surgical interference such as curetting. In such circumstances the parasite may grow actively and continuously with the formation of innumerable small bladders causing great destruction of osseous and other tissue. Moreover, the exogenous brood may have become so numerous and have travelled so far from their original parent that it is impossible for the surgeon to be certain that he has removed them all. If any cysts should have been left behind they will, in their turn, produce a fresh crop requiring further operation, and so on. In hydatids of bone, consequently, amputation will generally be found to be the necessary treatment. Such a type, therefore, from a clinical point of view well merits the term malignant hydatid disease, and we have dealt with it at some length on account of its clinical import.

Though we have distinguished between these three varieties—the simple cyst and those proliferating endogenously or exogenously—yet it must be remembered that the distinction is not absolute. Between the simple single cyst and one densely packed with countless daughter bladders every degree of complexity in the contents is met with, and the same primary bladder may, at the same time, shew both the endogenous and the exogenous methods of proliferation. An example of this is shewn in Fig. 227, where a visceral hydatid of the endogenous type has given rise to exogenous buds. So, too, in the hydatids of bone, where the favoured type is exogenous, it is found that when by penetration of the osseous substance the parasite can extend itself into intermuscular septa or other potential spaces these extensions are apt to, though they do not always, assume the endogenous habit. As a practical rule we may assume that hydatids of the viscera in man, which are those of most frequent occurrence, are of the endogenous form; while in bone they are usually, and in the brain and other extra-visceral localities frequently, exogenous. While it is rarely possible to

distinguish clinically between these varieties, yet from the point of view of operation it is a very much easier and simpler matter to deal with a single bladder with its self-contained contents than with an aggregate of many separate, and sometimes widely separated, cysts that have been formed by exogenous growth, and this is especially true in that class of hydatid to which we have referred as the burrowing type.

The rarer, more dangerous, and less understood form of parasite known as *Echinococcus alveolaris* sive *multilocularis*—alveolar or multilocular hydatid—differs in so many important aspects from the hydatidose kinds that it will be necessary to deal with it in a separate section. We may, however, observe in this place that, in view of its many striking differences, both pathological and clinical and, probably, zoological, which distinguish this variety, it is unfortunate that the term multilocular has, by long usage, become identified with it. There are hydatidose echinococci which are multilocular in the literal sense of the word, and have nothing in common with the alveolar hydatid save that they are both many-chambered. It would, therefore, be advisable not to use this name as a specific synonym for the alveolar form, which would then be known solely as the *Echinococcus alveolaris*. The term multilocular might then be retained in its proper signification as simply descriptive of a many-chambered character in whatsoever form of parasite this feature might occur.

*Sterile Hydatids.*—Some hydatids contain no scolices, and the absence of scolices is frequently associated with the absence of daughter bladders—they are in fact sterile, and constitute the structures described as acephalocysts by Laennec. We cannot enter into a discussion of the manifold causes of this sterility, the frequency of which may easily be exaggerated from failure to find the evidences of reproduction. Juvenility, senility, inherited debility, and degenerations in the parasite itself are conditions which, as in other organisms, may play their part; but probably the supply of nutriment is the chief, the vascular and other conditions of the adventitious sac or of the surrounding tissues being important factors in this respect. Thus, certain pedunculated hydatids of the peritoneum, which are attached to the mesentery by extremely long and attenuated pedicles, have been found sterile or nearly so. On the other hand, if the production of daughter-cysts be taken as evidence of fertility, it is remarkable that in the case of a hydatid bladder found lying free and naked in the peritoneal cavity these structures existed in abundance. Again, hydatids in the brain are said to be more frequently sterile than in other parts; this may be related to the occasional absence of the adventitious sac, or to a tenuity of it so extreme that it is unrecognisable as a separate structure.<sup>1</sup>

### Conditions Determining the Prevalence of Hydatid Disease.<sup>2</sup>—

<sup>1</sup> Scolices or hooklets were observed in eighteen out of ninety-seven cases of hydatids of the brain (47).

<sup>2</sup> It will be understood that this section refers to the hydatidose form only.

The parts played by the dog on the one hand, and by man and the domestic ungulates on the other, have been more precisely indicated in the paragraphs relating to the life history of the parasite. The mention of animals so closely associated with the domestic and economic life of man, as essential factors in the genesis of a serious human disease, thus becomes a matter of prime importance. It is necessary, therefore, to examine more closely the experimental and other evidence which has not only led us to connect the prevalence of the disease in man with the dog and the domestic animals, but has also furnished us with precise biological results.

So far as is known the *Tænia echinococcus* has only been found in the domestic dogs, the wolf (Cobbold), the jackal (Pancieri), and the Australian wild dog (*Canis dingo*) (von Linstow). This last, however, is probably not, by itself, a factor of great importance in the prevalence of hydatid disease in the Australian states, for though pure bred dingos are sometimes kept in domesticity by the aborigines, they are only to be met with in far-outlying districts where the white population is scanty. On the other hand, many parts of the country are overrun with the hybrids resulting from the crosses between the dingo and various breeds of domestic dogs, and in these there can be no doubt of the presence of the tapeworm. The assertion of an eminent helminthologist (Kuchenmeister) that man himself may be the host of this *Tænia* remains unsupported. As the wolf and the jackal are not, as a rule, brought into relation with man,<sup>1</sup> the domestic dog remains as the chief host of the sexual worm.

On the other hand, the bladder stage of the parasite is much more widely distributed; it has been found in man, various kinds of monkey, lemur, sheep, ox, pig, deer, camel, guinea, horse, ass, zebra, kangaroo, squirrel, seal,<sup>2</sup> cat, it has also been found in the turkey and peacock. Of domestic animals the sheep, ox, and pig are the principal intermediate hosts of the larval or bladder stage, and of these there can, we think, be little doubt that the sheep occupies the predominant place as the principal source of supply of the bladder worms to the dog. This point will be further dealt with in connexion with the geographical distribution of hydatid disease.

It has been proved, by feeding experiments conducted with all necessary precautions, that hydatid bladders or scolices from sheep and cattle when administered to dogs produce *Tænia echinococcus* and *Tænia echinococcus* only—in the intestines of the latter. Similar results have followed the administration of hydatids or scolices obtained from man. It has been also experimentally proved that proglottides or ova of *Tænia echinococcus* administered to some at least of the domestic animals give rise to bladder-worms.

<sup>1</sup> Sir P. Manson has pointed out that in India (where hydatid disease is rare) the jackal is in intimate relation with man, being a constant visitor in all towns and villages.

<sup>2</sup> A species of *Arctocephalus* that fed in the Zoological Gardens, Adelaide.

<sup>3</sup> A very copious list of the various helminthic parasites found in different animals is given in von Linstow's *Compendium der Helminthologie*, 1878, with Supplement 1887.



The conditions favourable to the prevalence and spread of hydatid disease appear, therefore, to be the following:—

1. A sufficiency of dogs infected with *Tœnia echinococcus*, by which means the supply of ova is kept up.<sup>1</sup>
2. Many animals, such as the domestic herbivora, particularly sheep, capable of serving as the intermediate host of the bladder-worm.
3. Conditions favourable to the entrance of the tœnian ova into the alimentary canal, either of man or of the ordinary intermediate hosts.
4. Facility of access of dogs to the carcasses, or hydatid-containing organs, of the intermediate hosts, such as the domestic herbivora, by which means the supply of *Tœnia echinococcus* is kept up.

So far as they go, statistics shew that these prescribed conditions are actually fulfilled in localities where hydatid disease is most prevalent. As will be seen later, Iceland and Australia stand out pre-eminently in this respect, especially certain parts of the latter.

An estimate of the number of dogs to the population in various localities gives for England one dog to fifty inhabitants; for France one to twenty-two; Belgium one to eighteen; Iceland one to eleven (35), a proportion for the latter country increased by Krabbe to one to three or five inhabitants. The essential point, however, is not so much the number of dogs as the number infected with the *Tœnia*, and in this respect there is, of course, much greater uncertainty; but of 100 dogs examined by the last-named observer in Iceland twenty-eight were found to contain them.

To the influence of the other factor concerned in the causation of hydatid disease in man, viz. the echinococcus-bearing herbivora, we shall return after speaking of its geographical distribution.

In Australia, though an estimate might be made of the number of dogs registered in the settled districts under the various Dog Acts of the colonies, such a record would leave out the enormous number, both in settled and outlying districts, which does not come under this head. There is no doubt, however, that the proportion of dogs to population is very great, and possibly exceeds that of Iceland; but, as already pointed out, the real factor for the spread of the disease is not the absolute number of dogs but the number that have become infected with the tapeworm, and it is certain that a very large proportion come under this category. Thomas indeed found that of the unregistered dogs in and around Adelaide, South Australia, 40 per cent were thus affected.

A more accurate estimate can be made of the number of sheep and cattle. The official returns of the various colonies shew that in 1892 there were in Australia as a whole about 3000 sheep and 300 horned cattle for every 100 inhabitants. No data,<sup>2</sup> however, exist for any

<sup>1</sup> When we remember that a single dog may contain many thousands of *Tœniæ*, and that each successively ripe proglottis holds some hundreds of eggs, it will be seen how wide may be the area of distribution of the latter by one host.

<sup>2</sup> From investigations made while this article is passing through the press, we are probably within the mark in saying that in the southern parts of South Australia, at least, 50 per cent of old Merino sheep are affected with hydatids.

precise statement of the proportion affected with the bladder-worm, but it is certainly large. Of 50 sheep examined, 22, or 44 per cent, were found infected in one or more organs.

We shall now consider the conditions which favour the entrance of the *tænian* ova into man or the domestic herbivora, and conversely of the bladder-worms into dogs, as they exist in Australia, with which country we are most familiar.

The explored parts of the country are stocked more or less heavily with sheep and cattle; many districts are overrun by dogs, not only by the dingo, but by domestic dogs that have "gone wild," and by cross-breeds resulting from the interbreeding of these among themselves and with the dingo. Large packs of such mongrels accompany every wandering band of aboriginals. The result is that an enormous destruction of stock takes place in spite of the costly, though too often spasmodic efforts in the direction of "vermin destruction";<sup>1</sup> it must be remembered also that the kangaroo is an intermediate host, but its numbers have so largely diminished in recent years that it cannot now be a factor of importance.

Moreover, and this is a matter of great consequence, in the vicinity of bush habitations the offal of the carcasses used for food-supply is too often carelessly thrown aside, and affords frequent opportunities for the bladder-worms to reach the intestines of the dog; the abundant ova of the resulting tapeworm, deposited with the *fæces* on the ground or herbage, or reaching the water-supply, may in their turn find their way into the bodies of the intermediate host.

In the water-supply, in fact, we probably have the explanation of the chief source of infection of man himself. In many parts of Australia this consists largely either of permanent swamps (as in certain parts of Victoria and South Australia where *hydatids* are particularly common), or, more frequently, of water-holes, natural clay-pans or excavated reservoirs, all of which, after rain, receive the washings of the surface. Not only do the dogs have access to these surface collections, often obviously contaminated, but the water is drunk both by man and beast—by the former, frequently and sometimes of necessity, without precautions to reduce the risks of infection.

Again, the use of imperfectly cleansed raw vegetables, in places where these are liable to be contaminated by the excreta of dogs, must be considered as a potential or actual source of infection.

When one remembers the affectionate, and we might add disgusting, familiarities with which pet dogs are treated, and the habits of dogs among themselves, it is not possible to ignore these animals as a cause of direct infection. A remarkable instance of infection in this way was reported by Dr. Cullingworth and Mr. Clutton, in which a lady, during a period of eight years, underwent repeated operations for *hydatids* in various pelvic and abdominal organs. The source of infection was a

<sup>1</sup> In South Australia alone, 7481 dogs, mostly dingos but partly cross-breeds, were destroyed in 1893 under the Vermin Acts.

pet dog that she had been in the habit of kissing and nursing, particularly when it was out of health; we are ourselves familiar with cases in which it is almost certain that infection has been received in the same way. These statements imply that hydatid infection is received through the alimentary canal, but, in seeking to account for the undoubted prevalence of this parasite in the lungs, the late Dr. S. D. Bird of Melbourne suggested that the tænian ova, blown by the wind in the frequent dust-storms of Australia, may gain direct entrance to the air-passages and there develop into a bladder. We have, indeed, seen the lungs of sheep containing hydatids lying free in a bronchus. But these cases cannot be regarded as proving this method of entrance, for in them cysts of an exogenous type existed in the adjacent lung-tissue, and it is quite possible that an exogenous bud may have pushed its way into the bronchus, becoming ultimately separated and free. Nevertheless, though unproved, we do not regard the former view as impossible.

It may be well, perhaps, to state here that there is no evidence to support the frequently expressed belief that the contents of echinococcus cysts themselves, when they occur in animals used as food, may, if ingested, give rise to hydatids in man. A doubt, however, on this point is implied by a remark of Posselt.

In Iceland, with which one of us is also familiar, though the physical conditions are widely different, yet there are the same necessary factors—many dogs, many herbivora, principally sheep, and contaminated pasturage or water; moreover there is in that island a closer bodily association between man and beast, and greater uncleanness in person and in the use of food and its appurtenances.

**Geographical Distribution.**—Though hydatid disease occurs in many countries, the published statistics, so far as known to us, do not permit of very precise statements of its comparative frequency; this is, with the exception of Iceland, perhaps more true of the old world than the new, as represented by Australia, the great prevalence of the disease in the latter country having compelled attention to it.

Quite uninfluenced by climate in itself, the spread of the disease appears to depend entirely upon the degree to which the factors mentioned in the preceding section are present.

Dealing first with Iceland and Australia, the two chief homes of hydatid disease, the absence of comprehensive statistics invalidates all exact numerical statements; still, enough evidence is forthcoming to support the general tenor of the previous statement as to the remarkable prevalence of the disease in these countries.

*Iceland.*—Estimates of the total number of the population affected vary from  $\frac{1}{16}$ th to  $\frac{1}{8}$ th. If we suppose the former to be too high an estimate, the frequency of the disease is evident nevertheless. Thus Schleisner, who seems to have been the first to indicate the parasitic nature of a disease that had long been known in the country under such names as hepatalgia, infarctus, obstructio, or hypertrophica hepatis, found that about  $\frac{1}{8}$ th of the 2600 sick who appeared in the medical reports of

the island, and  $\frac{1}{3}$ th of the 327 sick under his own immediate care, were affected with hydatid disease. On the other hand, Finsen, after nine years' experience, states that of 7539 cases, 280, or nearly 1 in 27, suffered from hydatid disease. This latter figure accords sufficiently nearly with the estimate by Galliot, that the number of the population affected may be reckoned at about  $\frac{1}{25}$ th. We are not aware that any case of alveolar hydatid has occurred in this island where the hydatidose form is so common, and it is also remarkable that the latter seems not to occur in the Faroe Islands, although they lie in the direct line of communication with Iceland, and possess plenty of dogs and sheep.

*Australia.*—Although Australia as a whole enjoys an unenviable reputation for the prevalence of hydatids, this disease does not by any means occur with equal frequency in the several states, or even in all parts of the same colony. Whether reckoned on the basis of the ratio of the registered deaths from this cause to the total mortality, or on the proportion of the admissions of persons suffering from hydatids to the total number of patients received into the various hospitals, the disease is found to be most frequent in South Australia, somewhat less so in Victoria, while New South Wales, Tasmania, Western Australia, and Queensland follow with a diminishing ratio in the order named. In North Queensland and in other northern parts of Australia the disease is practically unknown. This statement is based on returns, specially sought for, up to the end of 1896, covering over half a million of cases of admissions to various hospitals. The region of Australia, however, which yields the largest proportion of cases is that comprising the south-eastern part of South Australia and the contiguous western district of Victoria—a well-stocked and comparatively cool region, with much permanent surface water, often in the form of swamps. The returns, extending over many years, of the Mount Gambier Hospital, situated in one of the few districts in Southern Australia where permanent swamps exist, shew one hydatid patient for every sixty-five admitted for all complaints, these figures are probably not exceeded in any other locality. It is remarkable, however, that no case of the alveolar form has been recorded in any of these states or from New Zealand.

*New Zealand.* From the most recent available reports (2, 29), hydatid disease appears to be not very common in the North Island, but is more so in the South, especially in Dunedin and its neighbourhood, where hospital statistics shew that it is on the increase. It is remarkable that it is practically unknown amongst the Maoris, who keep many dogs and are not careful in feeding them (29).

*Great Britain.* Cobbold and others, who have endeavoured to ascertain the degree of prevalence of hydatid disease in the United Kingdom, have found a difficulty in basing any reliable estimate upon the defective data provided by the returns of the Registrar General's department (We should add that we are referring to a period prior to 1880). As the circumstances in which we write have made it impossible for us to investigate the later years either of the Registrar General's or of hospital

statistics, this section of our article must be necessarily incomplete. Nevertheless the following statements may be taken for what they are worth :—

Thomas quotes figures, derived from the Registrar-General's statistics for the decennial period ended 1880, which shew one death from hydatids to 11,876 deaths from all causes. As the result of a special inquiry addressed by the same writer to various British hospitals (replies having been received only from the London Hospital and one other), it was found that in the former institution, during a period of five years, twenty-four cases of hydatid disease were treated out of a total of 13,297 *medical* in-patients—a proportion of 1 to 554; while from the published reports of three Metropolitan hospitals—St. Thomas's, St. Bartholomew's, and St. George's—he derived, from the aggregate of figures, a corresponding ratio of 1 to 1124, the proportion varying considerably in the several hospitals.

Among 2100 necropsies at the Middlesex Hospital between 1853 and 1863 Murchison found hydatids in thirteen instances only; that is, one in 161 cases. He further stated, as the result of investigations at the Royal Infirmarys of Edinburgh and Glasgow, that hydatids are much rarer in Scotland than in England.

The limited area to which these various figures apply, and the wide discrepancies in them, render them of little value. Still, here and there a useful comparison may be made with other statistics.

In *Germany*, and, according to Leuckart, in the central and northern parts especially, the disease is not infrequent; Mecklenburg and Pomerania are declared by other German writers (30) to be the provinces where the hydatidose form is especially prevalent. From recent writings it appears to be fairly common in *European Russia*, where it is stated to occur concurrently with the alveolar form. So also it is found, with probably less frequency, in *France*, *Austria* (some parts), and *Italy*: it is stated to be common in *Turkey*, a country noted for the number of uncared-for dogs. In *Switzerland*, as we shall shew, it is the alveolar form which is prevalent.

*Asia*.—The disease is said to be not infrequent in the *Caucasian Province*. In *British India* it is rare, and particularly so amongst the indigenous inhabitants. In the *Philippine Islands* we have it, on the authority of Dr. R. P. Strong, Superintendent of the U.S. Biological Laboratory, Manila, that hydatids are almost unknown.

In *China* hydatids must be extremely rare, for we have been informed by Mr. James Cantlie, formerly of Hong Kong, that, out of upwards of 40,000 cases seen by him in that country, one only was of this nature; it occurred in a European, and apparently was not of endemic origin.

In *North America* the disease is decidedly uncommon; up to July 1, 1901, Lyon was only able to record 241 cases for the whole of the *United States* and *Canada*, and several of these occurred amongst the Icelanders settled in Manitoba.



*South America.*—In the *Argentine Republic* hydatids must be rather common, for Vegas and Cranwell report 970 cases occurring in the provinces of Buenos Ayres and Rosario only, during the twenty-five years ended 1900. These writers also state that 40 per cent of the cattle and sheep are affected, and 60 per cent of the pigs.

*Africa.*—Hydatids are stated to be not uncommon in *Egypt* (29A) and *Algeria*. In *Natal* they must be very uncommon, for, in surgical and pathological work in that country, extending over more than a year, our colleague, Professor Watson, saw no case either in Europeans or Kaffirs.

From *Cape Colony* a leading medical practitioner (Dr. Fuller), who had made special inquiries on the subject, informs us that human hydatids are neither common nor on the increase. On the other hand, the chief veterinary surgeon writes that in sheep and cattle they are fairly common, and that he has met with them several times in indigenous ungulates.

In speaking of the conditions which determine the prevalence of hydatid disease, we hinted that, of the domestic animals subject to these parasites, the sheep should be regarded as the predominant factor whereby the stock of *tænia* in the dog is kept up. This view was held by Madelung as the result of his investigations in Mecklenburg, and an identical opinion is expressed by Posselt (53); both these writers further state that the fine-woolled sheep, such as the Merino, are more liable to echinococcus disease than the coarse-woolled varieties. The survey of the geographic distribution of hydatid disease, and particularly as regards Australia, lends support to this opinion so far as it implicates sheep generally.

In all these countries where hydatids are notably prevalent we find sheep in large numbers relatively to other stock. This is the case in Iceland and in the German provinces of Mecklenburg and Pomerania where the disease is common.<sup>1</sup> Australia, which has always been noted in this respect, and the Argentine Republic, which appears likely to acquire a similar reputation, are, no doubt, noted for the extensive development of both the sheep and cattle industries. But if we examine the distribution of hydatids in the former of these countries, treating it as a whole, we find that the great majority of cases come from the southern and eastern districts, where the sheep largely predominate, while in the northern regions, where cattle-raising is the principal pastoral pursuit, almost to the exclusion of sheep, the disease is either absent or very rare. We are unable to speak of any similar localised distribution in the case of Argentina, and, unfortunately, Vegas and Cranwell, in their recent work, do not discriminate between the number of sheep and large cattle affected. Nevertheless, it is the case that the country contains an immense number of sheep.

On the other hand, hydatids are, as has been stated, rare in Natal where the number of cattle is large in proportion to the sheep, and the

<sup>1</sup> Speaking of the first named of these localities, Hjaltalin estimated that evidence of hydatids were to be found in every fifth sheep.



same holds good for India and the Philippine Islands. We must note also that the hydatidose variety of echinococcus is very rare in those European regions comprising Switzerland, parts of South Germany, and the Austrian Alpine regions, where the alveolar form prevails and the cattle-rearing industry almost exclusively exists.

Apart from the numerical influence of sheep in furnishing the supply of bladder-worms, there is, no doubt, a co-operative factor in the circumstance that, as a rule, the tending and care of sheep involves the use and assistance of dogs to a much greater extent than does cattle-rearing, and thus the two necessary factors for the spread of the disease are, in the former case, brought into close conjunction.

**Age** markedly affects the incidence; for, though the disease has been met with in a child two years and one month old, and in a man of eighty-one, the mortality from hydatids in the Australian colonies, compared with that from all diseases, rises continually through each decade of life till fifty years of age, and then gradually falls again.

**Sex.**—Out of returns covering 2307 cases of hydatid disease occurring in Australia in which the sex was clearly indicated, 1300 were males and 1007 females—a ratio of 100 to 77 (returns to 1894 inclusive). This increased liability of males is probably the rule; and is, no doubt, due to the occupations of men, and their predominance in numbers over the opposite sex in regions where the conditions are most favourable to the existence of the disease. Still, an exception appears to exist in the case of Iceland, where it has been stated that more than twice as many women as men have the disease. In Iceland the habits of life of the people are such as to expose women more to infection.

**Pathological Anatomy.**—The general features and varieties of hydatid cysts have been briefly indicated in the account of the life-history and development of the parasite. In this section it is proposed to add a few details.

It is generally admitted that, for hydatidose echinococci, there is only one true larval species, and that the special characters of the surrounding tissues, in which the hexacanth embryo has come to rest, exert a determining influence on its further development in respect of its size, shape, and mode of reproduction; or, in other words, on the special characters which it assumes.

In man the most usual form is that of a mono-cyst developed from a single embryo; a plurality of such cysts often coexists in the same individual, or even in the same viscus (multiple hydatids); and is referable to separate and not necessarily simultaneous parasitic invasions. In man such cysts often attain an enormous size, and, as we have shewn, may give rise to a numerous progeny of daughter or even grand-daughter bladders situated internally.

The less common form is that in which the original cyst, resulting from a single embryo, by repeated external proliferation produces a more or less compact cluster of vesicles, which are always comparatively

small, and often very minute ; in the multitude of these the identity of the parent cyst may be lost.

*The Adventitious Capsule.*—An aseptic foreign body embedded in an organ excites by its presence a cell-proliferation in the surrounding connective tissue ; the presence of a similarly situated parasitic cyst evokes a like response. We must, however, note that there is this difference between the two cases : while the physiological efforts of the tissues are directed towards the expulsion, disintegration, or encapsulation of the ordinary foreign body, the presence of the unbidden living guest is borne with tolerance, the relationship between host and parasite being, as we have said, one of symbiosis. In this the adventitious capsule is the immediate source from which the latter draws its nutrient supplies. The pressure induced by its continuous expansion, however, calls into existence an opposing factor which antagonises the tendency to cell-proliferation ; and, by a maintenance of equilibrium between irritative hyperplasia and pressure-atrophy, the capacity of the capsule increases step by step with that of the essential cyst. Nevertheless it must be admitted that in certain cases all signs of irritative hyperplasia are absent ; and that as an aseptically detached appendix epiploica sometimes excites no reaction in the peritoneal cavity into which it falls, so an echinococcus vesicle which has escaped from elsewhere may remain naked and free.

Again, in the exogenously developed cysts which affect the bones, the adventitious capsule may be, and indeed usually is, represented by no more than an extremely attenuated endosteal membrane. So, also, in the brain where a similar type occurs the cysts, if they lie, as they sometimes do, free in the ventricles, have no other adventitia than the ependyma of the cavities, or, if in the substance of the brain, than an extremely thin layer of the very slightly altered nervous tissue. It has also been noticed that the adventitious capsule of hydatids lying in the intermuscular planes of very mobile and greatly used parts is of such tenuity that it may easily be overlooked. On the other hand, in more exposed situations it may attain a considerable thickness.

In structure the adventitious sac is, in juvenile cysts, both cellular and vascular. In older living cysts it is formed of fibres and flattened cells shewing a stratified arrangement, which, as the inner surface is approached, become fused, condensed, and more or less destitute of cellular elements. The inner face of a healthy young sac, while it is still growing, is smooth and of a faint pink colour, though like serous membranes it is liable to both pyogenetic and non-pyogenetic inflammation, but we have not been able to satisfy ourselves of the existence of the alleged internal cellular layer ; in thick-walled (old) capsules there is a pale ochreous deposit adherent to its inner surface. So also, though in young cysts a certain amount of vascularity may be noticed, we have not, in a large series of cases, observed the varicose condition of the capsular vessels which has been said to give rise to dangerous bleeding after removal of the essential cyst. Indeed we have no experience of this event.

The shape of the sac, to which that of the enclosed parasite corresponds in virtue of the internal pressure to which it is subject, tends to assume a spheroidal form; when, however, its uniform expansion is interfered with by inequalities in the density of the surrounding tissues, it acquires a more or less irregularly sacculated shape. If the mutual pressure of adjacent parasites upset the equilibrium between hyperplasia and atrophy in the intervening partitions, the sacs coalesce into a compound sacculated capsule in which a separate parasite occupies each pouch. When the unequal resistance of surrounding parts is supplemented by a special inherent tendency of the parasite to grow in certain directions, a compound sacculation, extending even to separation, ensues.

*Extra-capsular Effects of the Growth of the Parasite.*—The connective tissue of the affected viscus survives the more highly organised parenchymatous elements, such as the liver-cells; but in the uninvaded parts the latter undergo a compensatory hypertrophy, and whenever this is observed in one part of an organ it should never fail to excite suspicion of the presence of a parasite in another. When the growing parasite comes to abut on the serous capsule of the viscus a fusion of its own adventitia with the latter takes place, and the combined structure may, as is usual in lung hydatids, become further adherent to adjacent serous surfaces, but it is remarkable that in hydatids in the abdomen, even though very large, such adherence may never occur unless there has been some surgical operation or traumatism.

*Degenerative Changes in the Capsule.*—With increasing age the adventitious sac is apt to undergo degenerative changes; these may be of an aseptic character, such as sclerosis or even calcification, due to the deposition of lime salts—phosphate and carbonate; or the latter condition may lead to the formation of foci of a degraded kind of bone. Usually these changes do not affect the capsule uniformly, but occur in patches of varying size, and may lead to enormous thickening. In a case of splenic hydatid at the Adelaide Hospital this calcareous and, to some extent, osseous transformation had proceeded to such a degree that the use of a small saw was necessary to effect an opening.

Again, changes of a septic character may take place, either spontaneously from unexplained causes, or as the result of surgical interference. Thus, we may have suppuration, ulceration, putrefaction with evolution of gas, and even gangrene.

Being a product of the connective tissue of the host the capsule may be invaded by pathological changes affecting the viscus in which the parasite is embedded; in this way it has been affected by carcinomatous and lardaceous disease.

*The Echinococcus Bladder.*—The structure of this organism has already been described. The lamination of the elastic cuticle, or ectocyst, a characteristic feature of the bladder-worm even at a very early stage, becomes with increased age still more conspicuous by the formation of fresh layers; till, in the mother cyst, it may reach a considerable though not necessarily a uniform thickness. So characteristic, indeed,

of hydatid cysts is this structure that, in the absence of all other definite products, the discovery of a minute fragment, which may be obtained by the hypodermic needle, renders the diagnosis absolutely certain.

*The fluid* which occupies the interior of normal living hydatid bladders and keeps their walls at a considerable degree of tension, is clear, limpid, and transparent, sometimes shewing a faint opalescence by transmitted light. The specific gravity ranges round 1010 and the reaction is usually neutral, though it may incline to alkalinity or even, it is stated, to acidity. It contains about 98.5 per cent of water and, of the solid constituents, about one-half is chloride of sodium; hence it gives a plentiful precipitate with silver nitrate. In the remaining solid matter there may be present traces of dextrose even in cysts situated elsewhere than in the liver, cholesterin, haematoidin, succinic acid (in combination with sodium and calcium), leucin, and tyrosin. Albumin exists in such minute quantities or in such a form that it is not precipitated by heat and nitric acid, but notwithstanding the fluid is very readily putrescible. In dying or dead cysts, however, the fluid may become albuminous. In cysts of the kidney there have been found products referable to the urinary constituents, such as urea, uric acid salts, and triple phosphate, and in this connexion we may remember that all the materials of the parasite must have been derived from those of its host. Lastly, it is to be noted that hydatid fluid contains a varying amount of some poisonous substance, originally described as a ptomaine, but which we may now doubtless call a toxin. This, when injected into animals, has been shewn to act as a cardiac poison, producing diastolic standstill, lowering of blood-pressure and temperature, as well as other symptoms. Absorption of a small dose of this poison is no doubt responsible for the urticaria that has so frequently been observed to follow the escape of hydatid fluid into serous cavities. The absorption of a larger quantity will similarly explain the peritonitis and the severe cardiac symptoms, leading sometimes to fatal collapse, that have also occurred with a frequency sufficient to serve as a warning against any unnecessary proceedings—even against so apparently trivial a step as aspiratory puncture—that may lead to the escape of this fluid, and possibly to its direct entrance into a vein. We shall speak elsewhere of the further risk due to the dissemination of brood capsules, scolices, or daughter bladders.

Chitin is the chief constituent of the external laminated enveloping capsule, though it is said to differ slightly from the ordinary chitin of invertebrates, and also to vary in composition with the age of the cyst (Leuckart).

In the contents of dead or dying cysts there may be serum, bile, or blood. The withdrawal of a transparent fluid, therefore, which yields to the ordinary tests no albumin, or but a trace, and gives a copious precipitate with argentic nitrate, affords strong evidence of its derivation from a hydatid cyst; but, as elsewhere stated, on account of the identical appearance and reactions of some other normal or pathological fluids of

the body, absolute reliance cannot, in certain cases, be placed upon these tests alone; and the detection of one or other of the biological products then becomes the only certain means of determining the parasitic nature of the tumour. Sometimes these are not forthcoming.

*Causes of Spontaneous Death.*—Dead hydatids are found more frequently in the liver than in other parts, both because the liver is the most frequently affected viscus, and because spontaneous evacuation *per vias naturales* is less easily effected than in viscera such as the lung and kidney.<sup>1</sup> Echinococcus cysts may die at any stage of their existence; and it is possible that, like other living things, they die on attaining a certain age. That this may be considerable is shewn by a case that came under our notice, where a living hydatid in the subcutaneous tissue had persisted for twenty-two years, having been taken during that period for a sebaceous tumour; there are cases of even longer duration on record. As a rule, however, disturbances of the obscure relations existing between the parasite and the tissues of their host anticipate the natural term of their life.

Several hypotheses as to the possible causes of natural death, all more or less unsatisfactory, have been suggested. It is said, for instance, that malnutrition, induced by diminished blood-supply, entails an aseptic death of the parasite; more especially when the latter has taken up its abode in the peripheral portions of an organ where the blood-supply is necessarily poorest.

Irruptions and transudations of the normal fluids of the body, such as blood, serum, bile or urine, are adduced as mechanical and toxic causes of death. Of these there can be no question as to the deleterious action of bile, and in our experience all dead cysts of the liver contain it or its derivatives.

Static shrinkage of the capsule, inordinate growth of an internal brood, are said to lead to a disproportion between the carrying capacity of the capsule and the contained parasite, which is inimical to its further development.

Whatever the causes of death, however, it is possible that they may be local rather than general, as the same individual may be the subject of both dead and living hydatids; even in the same viscus there may be cysts in widely different stages of degeneration, indicating death at different periods. Due weight must also be assigned to the suggestion that oft-repeated or long-applied traumatism, such as the continuous riding on horseback of stockmen, or perhaps, again, the toxic effects of the continuous use of noxious fluids as beverages, may eventually prove fatal to the life of the parasite. Probably amongst these latter must be included the inordinately strong, and often decocted, tea which the Australian bushman drinks so often and so copiously.

The effects of *rupture of hydatid cysts* into various cavities and passages

<sup>1</sup> Out of thirty-six cases which, on autopsy at the Adelaide Hospital, were found affected with hydatid disease of the liver, ten were the subject of retrogressing cysts that had not been suspected during life.



of the body, or even externally, will be described in the clinical section. They lead sometimes to spontaneous elimination of the parasite and a consequent relief of the host; but more often to urgent symptoms which require prompt surgical interference. Rupture of a healthy bladder may result from undue compression or other violence, or from pressure-atrophy, due to expansion of the cyst, the thinned intervening tissues giving way at the weakest spot; but most frequently it is the consequence of localised ulcerative changes in suppurating cysts.

*Hydatid cysts that die and undergo spontaneous retrogression become the subjects of a very constant series of degenerative changes, which may be described in the following stages:—*

1. *Stage of Turbidity.* The fluid of the mother cyst becomes turbid from the precipitation of the albumins of the nutritive pabulum, which being no longer absorbed and metabolised by the dying or dead parasite, are suspended in the fluid, causing it to become albuminous. A similar transudation of serous fluid and refilling of the sac, or possibly of the cyst itself, may take place after tapping. Thus far there are no changes in the adventitious sac, and the contents of the daughter cysts are still clear.

2. *Fatty Stage.* These precipitated proteids are converted into fatty substances resulting in still greater turbidity of the fluid. At a later period the liquid contents may assume the consistency of a butter-like sinagma. The mother cyst acquires a gelatinous or gummy aspect, and from shrinkage in size is thrown into folds (see Fig. 228); the daughter cysts also shrink, and their contents in turn become turbid. Though the daughter cysts undergo precisely the same series of changes as their parent, the former are, generally speaking, a stage behind the latter in their transformations.

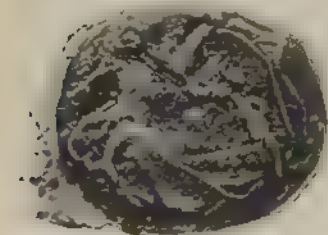


FIG. 228. Section of retrogressing human hydatid cyst. Inside the shrinkage of adventitious capsule is the collapsed, unexpanded Echinococcus bladder, which has assumed a gummy consistency. The contents have been converted into a caseous, granular mass. Photograph half the natural size.

3. *Stage of Desiccation.*—There is complete opacity and marked desiccation of the contents, which are represented by a putty-like mass. Degeneration has proceeded in the mother cyst, which has now become a mass of gelatiniform shreds not yet completely opaque. The fatty transformation has extended to the production of crystals such as of stearin and cholesterol, and less frequently of other crystalline forms of obscure nature and uncertain composition, among these Charcot's crystals may be mentioned.

4. *Stage of Calcareous Infiltration.* Infiltration of lime salts—carbonate and phosphate—which has previously begun in the adventitious capsule, becomes general in the whole mass. We have also seen in the calcifying



capsule patches of a very degraded form of bone. The putty-like substance slowly disappears with a corresponding shrinkage, and the parasite is now represented by a semi-calcareous mass in which are embedded the shrivelled and opaque remains of the mother and brood.

In a further stage, seldom reached, even these membranous débris may lose their identity, the hooklets only remaining to indicate the true nature of the now wholly calcareous mass.

*Presence of Bilirubin.*—In a certain number of cases of liver hydatids the mother cyst, its liquid contents, and—at a later stage—the daughter cysts also, may become stained a green or orange colour from irruption or transudation of bile, which most frequently takes place between the adventitia and the mother cyst, though it may involve the latter. When this is in excess it may give rise to the presence of amorphous masses of biliary matter or of bilirubin crystals, to which product attention was first called by Bristowe in 1853 under the name of hæmatoid crystals. In one case—an enormous cyst of the liver which had begun to suppurate—we found a mass of crystalline bilirubin, with traces of biliverdin, weighing 1·13 gramme: many of the daughter cysts were stained with a similar material. So far as we are aware, this substance has not been found in cysts other than those of the liver, a fact which indicates its biliary origin; further, in our experience, it occurs only in those cases where the parasite is dead.

*Papillomatous Growths in Hydatid Bladders.*—Besides the above series of changes, which constitute what may be called the usual pathological sequences of spontaneous death, various observers have noticed, projecting from the inner wall of cysts, otherwise apparently normal and containing large broods, peculiar raised papilloma-like excrescences, which occur in scattered patches of over an inch in diameter and of 2 mm. or more in height. Microscopically they consist of hypertrophic ingrowths, rather than infoldings, of the cuticle; and in one case they contained small daughter cysts with relatively thick walls. We have observed these papilloma-like growths in cysts which were diagnosed as belonging to the lung, liver, and spleen. Probably they represent abortive efforts at endogenous proliferation; a parallel condition is seen in the papillomatous overgrowths of the nacreous layer of pearl-shells, which produce a localised, sessile pearl formation. In some of these cases patches of the mother cyst were gelatiniform and of a transparent amber colour, as if vitality were lost and degeneration about to become general.

*Absence of Mother Cyst.*—Hydatids occasionally occur, in which, with every appearance of endogenous development, the mother cyst would seem to have entirely disappeared, yet, generally in such cases, traces of this structure may be discovered in the shape of gelatinous shreds which still shew their characteristic laminated structure. It is difficult to understand by what processes so substantial a membrane can be so extensively absorbed, macerated, or dissolved; yet this seems the only kind of explanation that can be offered. Such an example was an

enormous hydatid in the liver of a male subject, the contents of which measured 20 pints. On a calculation, based on an enumeration of the daughter cysts in a measured quantity, the total number of these exceeded 28,000 ; and this figure did not include thousands that were too small to be counted with the naked eye. Suppuration had not long commenced, but barely a shred of mother cyst could be detected. It was in this case that the aforesaid crystalline mass of bilirubin was found. The man recovered after incision and evacuation, and about three years afterwards was again successfully operated on, in a similar manner, for another large hepatic suppurating cyst, containing five pints, which presented no unusual features. No doubt the second cyst existed at the time of the first operation.

*The unequal distribution of hydatids in the various viscera* requires a short discussion of the circumstances which determine the ultimate destination of the wandering embryos. The conspicuous preponderance of liver cysts is attributed to a passive transportation of these embryos by the blood of the portal vein. The high, but relatively lower frequency of pulmonary hydatids is, on the same hypothesis of vascular transportation, generally explained by the fact that the travelling embryos can only reach the lungs after traversing the portal capillaries ; and the still less frequent presence of the parasite in other organs finds a similar explanation in the fact that the embryos on their way must traverse both the portal and pulmonary circulations.

It is difficult, however, on this hypothesis to account for the comparative frequency with which multiple peritoneal and omental cysts are found ; for we must then believe that these cases owe their origin to an arterial embolic shower of embryos which have successfully traversed the two capillary obstructions of the liver and lungs—unless we may suppose that they either work their way into the omental arterioles or enter the radicles of the omental veins, in which latter case they would have to reach their destination against the venous blood current. Now it often happens that the lungs have entirely escaped invasion, while a multitudinous cystic development is in progress in the peritoneum and omentum, an event which would not be probable if the embryonic swarm had passed through the lungs. To account for such a multiple dissemination three possible explanations present themselves ; we may suppose (i.) that it is possible for embryos, after having traversed the stomach, to reach the peritoneal cavity by gravitation or otherwise, there to develop into cysts which acquire their capsules by exudation from this membrane, and doubtless multiply by exogenous proliferation ; or (ii.) a shower of escaped and minute daughter cysts has become engrafted on to the peritoneal surface ; or (iii.) liberated scolices may themselves develop into cysts. While we can neither affirm nor deny the possibility of the first alternative, we are convinced of the occurrence of one or other or, possibly, of both the latter methods of dissemination. The cases coming under our notice that strongly support such a view are of this nature—a visceral hydatid has been operated upon in a way

that has permitted some escape of hydatid fluid upon the surfaces of the wound. Within a period varying from a few months to two or three years a crop of small bladders has developed in the connective tissue adjacent to the incision, or even in the scar itself. No other explanation seems possible than that either cysts, so minute that they have escaped observation, or scolices, or it may be brood-capsules, have become transplanted in the tissue, where they have undergone subsequent development. And if dissemination and transplantation occur in this way, there can be no reason to doubt this sequence when the daughter brood (or scolices) are liberated in the peritoneal cavity; indeed, in support of the possibility of such an occurrence may be adduced the cases, not unfrequently met with, in which the peritoneum and peritoneal surfaces of the abdominal organs, often in the most dependent positions, have been found studded with innumerable small cysts of such uniform size as to suggest a sudden and simultaneous invasion in this manner. In some of these cases there had been antecedent tapping. It is noteworthy, however, that the peritoneum does not always respond to the presence of the parasite in the same active manner, for the bladders may fail to acquire any adventitia, and thus remain entirely nude and free in the peritoneal cavity. Indeed, when we review the facts of distribution of this and allied parasites, as well as the failure to account for them satisfactorily by vascular transportation or other passive migration, we are disposed to lay the greater stress on a selective affinity, which seems to lead the parasite to certain situations. A like phenomenon is a special disposition, possessed by certain nude hydatids, to enlarge independently of the plane of least resistance, or even in direct opposition to it. In this way cerebral hydatids may perforate the bony cranial vault—an event paralleled in the behaviour of the *cœnurus*, which in a similar way perforates the skull of sheep, and so offers facilities for cure by puncture. It must, however, be borne in mind that the external appearances of a cerebral hydatid may be exactly simulated by a parasite of the cranial bones, which has caused absorption and thinning of their substance.

Even in the case of the liver another view than that of passive transference is possible, for it is possible that the embryos may bore their way directly from the one organ to the other.

Although there is, we believe, no direct experimental evidence in favour of the view that scolices, brood-capsules, or even daughter bladders may, when they escape from a parent cyst into a serous cavity, give rise to a crop of multiple hydatids,<sup>1</sup> yet, when we remember the difficulties of other hypotheses of transit, this supposition seems reasonable in the light of those cases that have been mentioned of multiple, and apparently simultaneous, infection of the peritoneum and of wounds. The possibility of such an occurrence should again warn us against any unnecessary proceedings, such as tapping, which might permit the escape of fluid.<sup>2</sup>

<sup>1</sup> Naunyn and Rasmussen have asserted that scolices and brood-capsules do sometimes change into hydatids (25, p. 634).

<sup>2</sup> For many references to this question, see Posselt (53, pp. 504 and 510).

In concluding this section we might mention that the very reasonable suggestion has been made by more than one writer, and supported by some evidence, that the local conditions of traumatism may be favourable to the harbouring and development of these parasites not only by producing a *locus minoris resistentiæ*, but also by affording a favourable nutritive nidus (cf. 8, 45).

### General Clinical Aspects of Hydatid Disease

Before proceeding to describe the symptoms, physical signs, diagnosis, and treatment of hydatids in the different organs of the body, there are certain general considerations, applicable to hydatids wherever situated, which may be advantageously discussed.

**Symptoms.**—In conformity with the comparatively slow growth of the parasite the surrounding parts usually so accommodate themselves to its presence that, even when of great size, it may occasion surprisingly little inconvenience. There may be a sense of fulness and weight, and an interference with certain movements of the body. Severe pain is accidental, and due generally to irritation of a nerve-twig by the enlarging capsule. Sometimes the pain is inflammatory in character, as when a pulmonary hydatid approaches the pleura and excites localised pleurisy, or an hepatic hydatid a similar peritonitis. At times a living hydatid is found in the substance of a lung, the seat of lobar pneumonia: in this case the same pain and other symptoms arise as in ordinary pneumonia, and the one complaint is almost certainly only an accidental complication of the other.

Symptoms due to interference with the function of an organ in which a hydatid is situated vary inversely as the ability of the organ to expand. If the organ can increase in size step by step with the growth of the parasite, as in the liver or spleen, there is very little destruction of tissue in its neighbourhood; and this may be balanced by hypertrophy elsewhere: the parenchyma is pushed aside, and so slowly as to permit of adaptation to its new conditions, with little or no diminution of its function. In the lung, which is confined within moderately resisting chest walls, as the parasite enlarges the breathing space diminishes; for the lung retracts as the growth relaxes the elastic pulmonary tissue. When, however, the retraction is complete, and the growth begins to exert a distinct pressure on the chest wall, this will yield before its advance, and bulge so considerably that the diminution of lung space will be less than the increase in the size of the tumour. Where, as in the brain, no expansion of the viscus is possible, pressure symptoms soon arise, though even here marked adaptation may take place; thus, in children, intracranial hydatids acquire a much greater volume without issuing fatally than in adults. When operated on they have been found to hold more than a pint of fluid, the bones of the skull having become so widely separated at their sutures as to allow the head to become very voluminous; or the bones may have yielded and enlarged, so as to produce a very noticeable prominence over a large area.

After a hydatid cyst has been punctured for purposes of diagnosis or treatment, an urticarial rash often follows within a short time. This is usually general, and lasts for a few hours or one or two days. It has also been noticed after the rupture of a hydatid cyst into one of the large serous cavities. It is probably occasioned by absorption into the blood of a poisonous substance present in normal hydatid fluid. So also a form of localised urticaria, or even a mild cellulitis lasting for one or two days, may follow escape of fluid into the subcutaneous tissue after the puncture of a superficial cyst. On suppuration of the adventitious capsule the symptoms are those of a large abscess of the organ infested by the parasite; sometimes there are repeated rigors, local pain and tenderness, and a continuous increase in the size of the tumour or organ manifest on careful examination. Suppurating hydatids have a marked tendency to rupture, or rather to open into neighbouring cavities; the symptoms, in these circumstances, vary with the direction of the rupture, whether into a bronchus, the bowel, the peritoneum, the pericardium, the urinary passages, or elsewhere.

**Physical Signs.**—On inspection there may be a slight but general bulging of the part, a markedly smooth and round local prominence, or if the parasite be multiple, a number of bosses may exist. Should a venous trunk be compressed, its cutaneous branches will be visible as dilated vessels. On palpation the tumour is found to be smooth and firm, sometimes elastic; in other cases it is quite hard, as though solid. Fluctuation can seldom be detected in hydatid tumours; this is due to the high tension inside the cysts. On percussion they are absolutely dull. In a certain proportion of cases they yield a hydatid thrill. This is a peculiar vibratory sensation perceived by the finger percussed, and when the cyst is large may be elicited over a considerable area. It is not, however, always present—in fact it is only found in a small minority of hydatids. Moreover, the same sign may be recognised in other cysts not hydatids, such as hydronephroses, ovarian and mesenteric tumours, and even in ascites. After withdrawal by aspiration of part of its contained fluid, a thrill has been obtained over a hydatid, from which it was previously absent. Probably for its production the cyst must be of a certain magnitude, its contents of a certain density, its wall of a certain thickness and tension, and its attachment to surrounding structures definite. These associated factors are more frequently found in hydatid cysts than in any others, hence the sign is most common in them; but even in them they are generally absent, and hence the sign is unusual. While, therefore, thrill is highly suggestive of hydatid, it is not pathognomonic; nor by its absence is the hydatid nature of a cyst disproved.

**Diagnosis,** often easy, is at times difficult, or even impossible. A rounded, firm, smooth, elastic tumour in an organ or part, free from pain and tenderness, without antecedent or present symptoms other than those due to its size, and yielding a thrill on percussion, is most probably a hydatid. The probability is increased in countries such as Iceland and Australia, where the disease is very prevalent. This element of



geographical distribution cannot be ignored. In Australia, for instance, the disease, under the most unexpected conditions, and from the most unlikely quarters, is continually surprising the physician ; so this possibility has constantly to be borne in mind. The Röntgen rays often afford reliable evidence of the presence of the parasite, either by the screen, or even more satisfactorily in a skiagram. This is especially useful when the parasite is located in the centre of the lung, so as not to yield surface indications on physical examination of the chest, or when extending upwards into the thorax from the middle of the dome of the liver. An increase in the proportion of eosinophil cells in a blood count has been suggested as confirmatory of the diagnosis of the parasite, but this has hitherto not proved of any practical value.

The question of the value and advisability of aspiratory puncture for purposes of diagnosis is one of importance, and has occasioned some difference of opinion. This proceeding has certainly often been performed without the slightest evil consequence, and has afforded an absolute diagnosis. Thus, puncture of a liver uniformly enlarged or of a tumour in the abdomen with a fine aspirator, trochar and cannula, or a long large hypodermic needle, has yielded a quantity of characteristic hydatid fluid, containing scolices, hooklets, or microscopic fragments of laminated membrane. But a negative result may follow and mislead. A hydatid, even of considerable magnitude, if closely packed with small daughter cysts, will yield no fluid, or so little as to be overlooked, and the tumour will be regarded as a solid growth. In these circumstances, if the contents of the syringe are blown out upon a microscope slide, a tiny fragment of hydatid cyst may be obtained from the needle, and will prevent error and make the decision positive and final. This should always be practised when the needle is used and the tapping is apparently "dry." Another source of uncertainty and fallacy exists. Frequently no hydatid structures are obtained, and we have then to depend on the character of the fluid. Unfortunately, as we have said, there are two liquids with which that from a hydatid is identical in appearance, and nearly so on chemical analysis, the cerebrospinal and that of some hydronephroses. When cerebral symptoms have pointed somewhat indefinitely to an intracranial hydatid, and on trephining the skull fluid has been withdrawn by a long hypodermic needle, it is a matter of serious moment, in regard both to diagnosis and treatment, to determine whether this has come from a dilated ventricle or from a hydatid. In the latter case an opening should be made in the brain substance for the removal of the parasite ; in the former such a proceeding is undesirable and might be fatal. We have no test at present to decide the question : both fluids are clear and watery, both contain sodium chloride and a trace of sugar. The same difficulty arises in respect of a renal cyst. Though many hydronephroses contain fluid evidently urinous, some yield a liquid exactly like that from a hydatid. If we are sure that the cyst lies in the substance of the liver or spleen, the exhaustion of fluid of a clear watery character decides the diagnosis ; but we cannot always be certain



of the situation of the cyst; for a right hydronephrosis is sometimes adherent to the under surface and margin of the liver, and at times physical signs leave us in doubt whether a tumour in the left hypochondrium and anterior lumbar region be in the left lobe of the liver, in the spleen, or in the kidney. When the lung is the seat of disease it might be thought impossible to err. But here we are confronted by another and special difficulty which may serve as an introduction to a consideration of the several dangers of aspiratory puncture. Numerous instances testify to the possible danger of withdrawing even a small quantity of fluid from a pulmonary hydatid. In consequence of this apparently trifling operation the cyst may burst, and its contents, rushing up the bronchial tubes, which frequently open directly and freely into the cavity in which it lies, may flood both lungs and drown the patient. Even if this fatal catastrophe should not occur, a most violent suffocative cough may be excited, with expectoration of blood and of such quantities of hydatid fluid as utterly to prostrate the patient even within a few minutes. And within two or three days there may be marked signs of septic contamination of the sac, such as pyrexia and the ejection of extremely fetid sputa. For these reasons we lay down the rule that no medical man should ever use a needle in his consulting-room to make a diagnosis in a possible pulmonary hydatid; nor should he attempt to draw off the fluid in a probable hydatid of the lung until he has excised a portion of a rib, and is ready for immediate incision directly its parasitic nature is established by puncture. There are other sources of danger in aspiration for diagnostic purposes. If the sac be on the surface of an organ such as the lung, liver, spleen, or kidney, or is situated in the omentum, and the serous surfaces covering it are not united by adhesions, the puncture may permit the more or less rapid leakage of the contents of the hydatid into the surrounding serous cavity, and scolices, brood-capsules, and minute daughter cysts may escape, and lead to a disseminated multiple infection with disastrous consequences. In not a few instances, too, this simple procedure has been followed by an immediate collapse of the patient, sometimes attended with profuse vomiting and purging, and proving rapidly fatal. This dread eventuality, which cannot be foreseen nor guarded against, is attributed to the sudden entry into the blood of an unknown but very potent toxin. A less serious but very distressing occasional consequence is a smart attack of urticaria with some elevation of temperature. For these reasons we deprecate any routine or unnecessary employment of aspiratory puncture in diagnosis, and if the other clinical methods at our disposal suggest the presence of the parasite, it is probably much safer and more satisfactory to make a small exploratory incision wherever practicable.

**Prophylaxis.**—The general nature of the measures calculated to prevent or at least to limit the spread of hydatid disease becomes evident from what has been said concerning the conditions which give rise to it. As the prevalence of the parasite in man depends primarily upon the number of dogs affected with *Tænia echinococcus* and the facilities

afforded for the entrance of the ova into the human body, it follows that laws which require registration of dogs, and the destruction of those which are not registered, are of the greatest service if vigorously enforced. These laws not only usefully restrict the number of all dogs, but also serve especially to limit the class of vagrant or ownerless dogs which, in the absence of regular feeding with wholesome household scraps, are liable to be infected by the offal of butchers' shops or abattoirs. The offal of such establishments should, in fact, be so disposed of that dogs cannot possibly obtain it. A further safeguard would be to abstain from feeding dogs with raw meat of any description; for the usual culinary methods of preparation are destructive to the life of the bladder-worms should they exist. Judicious cathartic and anthelmintic medication of dogs might also be of service, but it must be remembered that any such treatment must be accompanied by such a disposal of the excreta as will prevent further infection. Indeed, similar sanitary precautions should invariably be taken to render innocuous, by boiling water or other means, the excretions which accumulate about kennels or other places where dogs congregate.

The water-supply being, as we have said, the principal source of the disease in man, all those measures are efficient prophylactics which protect it from contamination with the tapeworm ova, which are liable to be blown into it by the wind, or carried thither by the washings of the surface. Boiling or effective filtration of the water may be regarded as absolute safeguards, and too great care cannot be taken in the cleansing of those ground vegetables which are eaten raw. It has been suggested that the ova may gain entrance into the lungs with the inspired air. In Australia, at least, where the facilities for infection exist to so great a degree, and where dust-storms are frequent, it is possible that such minute bodies as the ova might in this way gain entrance to the body; it is even conceivable that the secretions of the air-passages might possess a sufficiently corrosive or solvent action to liberate the contained embryo; but direct proof is yet wanting, and we may probably with safety regard the alimentary canal as the only channel of entrance to the body. We repeat that the bad habit of kissing pet dogs is dangerous in respect of the possibility of direct transfer of hydatid from beast to man, and disgusting in respect of some of the habits of the tribe.

It cannot be too emphatically stated that, for all practical purposes, the whole question of prophylaxis may be comprised in the statements, that if there were no dogs containing *Tænia echinococcus* there would be no hydatid disease; or that, if the source of supply of bladder-worms were entirely cut off, dogs would no longer be infested with *Tænia echinococcus*.

**Treatment.** — A great variety of remedial measures have been applied to hydatid disease, and these may be classified in two groups — those, namely, which aim at the destruction of the life of the parasite *in situ*, and those which aim at its removal.

1. Measures which aim at the destruction of the life of the parasite.

(a) *Internal administration of drugs.*—Of the various medicaments which have been used with this object it may be confidently asserted that they are absolutely useless.

(b) *Acupuncture.*—Long thin needles are inserted into the cyst, left there for ten or fifteen minutes, and then removed. This probably cures (when it does cure) by allowing the contents of the bladder to escape into adjacent cavities, such as that of the peritoneum in the case of the liver. Apart from the great uncertainty of the method, it is reprehensible on account of the possibility of a general parasitic invasion of the peritoneum by escaped scolices, a subject we have already discussed.

(c) *Electrolysis* probably acts not by virtue of the electric current, but of the acupuncture; and the practice is to be condemned accordingly.

(d) *Injection of fluids into the cyst after removal of some of its contents.*—The following have been employed:—Extract of male fern, carbolic acid, alcohol, solution of pepsin, potassium permanganate, tincture of iodine, mercuric chloride. None have proved efficacious.

(e) *Aspiratory puncture and withdrawal of fluid.*

2. Measures having the object of complete removal of the parasite.

(a) By means of an opening made with *caustics* (Récamier's method).

(b) Long-continued *drainage* and evacuation through a cannula inserted into the cyst and retained for a long period (*canule à demeure*).

(c) *Double puncture with small trochars, followed by incision* (Simon's method).

(d) Various forms of *direct incision* with immediate, or delayed, removal of the parasite.

Nearly all these methods are now merely matters of historic interest; two only require further consideration; the others having been proved to be either inefficient, or open to objections so serious as to have led to their abandonment. The two methods we shall discuss are aspiratory puncture and removal by direct incision.

*Aspiratory Puncture.*—Under antiseptic precautions, and by means of an aspirator needle, which should not exceed one-sixteenth of an inch in diameter (results having shewn conclusively the superior safety of a small needle as compared with larger sizes), as much fluid is drawn off as will flow. This simple and, as its advocates urge, safe procedure does undoubtedly cause the death of the parasite in a certain proportion of cases, and the consequent cure of the patient; indeed, this event may happen after withdrawal of a very small quantity of fluid, the dead organism then passing through the same kind of harmless retrogressive changes as it does when undergoing spontaneous cure. It must be remembered, however, that, although the aspiratory puncture may have

caused the death of the parasite, the tumour may quickly regain its former size. If now a portion of the fluid should be again withdrawn it will be found to be albuminous, the sac (or cyst) having become filled with serum, which may either be absorbed, with a resultant cure, or suppurate, the latter event being especially liable to occur on a further attempt to remove the fluid.

Notwithstanding the favourable results which have undoubtedly attended this method of treatment in many cases, some very serious objections are urged against it. In spite of its simplicity the operation is by no means devoid of danger; death, with cardiac diastole, has occurred in a considerable number of instances from the toxic effects of the absorption of the fluid, with such suddenness as to indicate its direct entrance into the vascular system; and extreme collapse, from which, however, the patient may gradually recover, is not infrequent. The operation is only likely to be successful in simple living cysts, or in those at any rate in which there are few daughter cysts—conditions which are quite undeterminable beforehand. In any case no assurance can be given that the operation will be successful, for the puncture frequently fails to kill the parasite, or, still worse, leads to inflammatory or suppurative changes. Even if its life be destroyed it remains in the viscus a bulky, dead organism, prone to decomposition with all its mischievous complications. This method is quite inadmissible in suppurating or ruptured cysts, and, indeed, we hold that its employment as a curative measure is strongly to be deprecated as unsound in principle, and in practice neither efficient nor safe.

In Australian practice, based upon a large experience, there is a marked tendency not only to abandon aspiration altogether as a curative means, but also, as far as possible, to limit its application even as a means of diagnosis.

*Removal by Incision.*—The operations included under this head aim at removal of the parasite, either at once or after some little delay. The particular method known as Lindemann's operation has been successfully adopted by Australian surgeons for some years. In this procedure the cyst and its contents are removed, at the time of operation, by an incision made through the most prominent part of the tumour, or, it may be, at some other spot from which the parasite is, on anatomical grounds, more conveniently accessible. The edges of the visceral wound, if not already adherent, as is frequently the case, are attached by stitches to those of the parietes of the body, so that the pouch or cavity formerly occupied by the parasite drains externally, hence the term marsupialisation applied to this method. Rarely is any difficulty experienced in the dislodgment of the mother bladder, which readily presents itself in the wound, and, so to speak, invites removal; moreover, it is remarkable how soon enormous cavities close up by adherence of the collapsed walls or by granulation.

This method of marsupialisation, though on the whole practised with a large measure of success in Australia and elsewhere, is, it must

be admitted, occasionally followed by certain inconveniences such as protracted recovery, long-continued suppuration, and, in the case of the liver, biliary flux, persistent fistulæ or immobilisation of important organs in a faulty position. Recognising these objections, Mr. Bond of Leicester, in 1891, advocated and practised a procedure for abdominal hydatids by which, after the removal of the bladder-worm, its cavity is carefully emptied, cleansed, closed by sutures, or even left unclosed and the viscus returned into the abdomen. The wound in the abdominal wall is closed as in an ovariectomy. This is an ideal method, but it is not always applicable; nevertheless suppurating cysts have been successfully treated in this way. Delbet has proposed the practice of obliterating, as far as possible, the cavity of the adventitious capsule by bringing its opposing walls together by sutures (*capitonnage*).

Still more recently Mabit of Buenos Ayres advocates the resection of as much as possible of this sac in addition to the return of the affected viscus into the abdomen. Discussion of the relative advantages of these and other methods of operation is, however, beyond the scope of this article, and must be sought for in surgical treatises. But we may again insist that the first principle of treatment is the complete removal, not the death *in situ*, of the parasite, and this can only with certainty be insured by some method of incision. Then remembering the dangers, already alluded to more than once, that may follow escape of the fluid contents in the form either of dissemination of daughter cysts, brood-capsules, or scolices, which may give rise to multiple infection, or of severe toxic action of other constituents, it is most important that the efforts of the operating surgeon should have regard to the possible occurrence of these contingencies. It is for such reasons, as well as for the risk of septic infection, that we have more than once deprecated the unnecessary use of aspiratory puncture for diagnostic purposes. In addition to the ordinary methods of diagnosis we now have the effective assistance of the Röntgen rays and of stereoscopic radiography, the value of which has been amply demonstrated. If all these means should still fail to reveal the existence, or site, of a hydatid cyst, it is, we are convinced, safer to make a small exploratory incision wherever this is possible.

The following propositions indicate the principles of the treatment of hydatid disease that are generally accepted in Australia:—

1. The objections to aspiratory puncture are that it is only applicable to a small class of cases; that even in these it frequently fails in its object; that it is in itself a possible source of danger, by inducing suppurative changes, or by permitting leakage of fluid with possible consequences that we have sufficiently indicated; and that, at best, it leaves the dead organism in place. In pulmonary hydatids there is a special risk of suffocative flooding.

2. Removal of the parasite by incision is an effectual and, with proper care, a reasonably safe proceeding; it should be the recognised and general practice.

3. No other treatment is justifiable in suppurating or ruptured hydatids, if we except those in which spontaneous evacuation by the natural channels is in progress and urgent symptoms absent, when probably the best treatment is to leave matters alone.

4. Lindemann's operation, in which, after removal of the parasite, the cavity of the adventitious sac is left to drain externally, has stood the test of a large experience with favourable results, and is probably the best and safest procedure for general application. Possibly, however, Bond's operation, or some modification of it, in which, after evacuation, the emptied adventitious sac is left behind, may prove to be more satisfactory in certain cases, the proper limits of which have yet to be determined by the test of experience.

### Hydatids in the various Viscera of the Body

**Distribution of Hydatids in the Body.**—In 1000 autopsies performed in the mortuary of the Adelaide Hospital, South Australia, forty-nine bodies contained hydatids, that is, about 5 per cent. Eleven of these were cases of multiple hydatids; in five, two organs were infested; and in six, three or more of the viscera. In thirty-six instances the liver was involved; in nine the lungs; in six the spleen; in five the kidney; in five the peritoneum; in four the brain, and in one the heart. In a more extended table compiled by Thomas, comprising for all countries nearly 1900 cases, the frequency with which different organs are attacked is shewn by the following percentages: liver, 57; lungs, 11·6; kidney, 4·7; brain, 4·4; spleen, 2·1; heart, 1·8; peritoneum, omentum, and mesentery, 1·4.

**Hydatid of the Liver.**—*Symptoms.*—There may be aching about the right shoulder, and if the hydatid be large, a sense of weight and distension about the right hypochondrium. Actual pain is rare, but enlargement upwards into the chest has caused a severe paroxysmal neuralgia, and when suppuration supervenes it is often acute, and an excruciating hepatic colic attends the passage of membranes along the bile-ducts. The functions of the stomach and bowels are seldom interfered with, even when the cyst is so large as to fill and distend the abdomen. Not infrequently, at an autopsy, a parasite of no small size is discovered, which has occasioned no symptoms during life, or none sufficient to attract attention.

*Physical Signs.*—These will vary with the size and situation of the parasite: if it be small and deep-seated they will be absent. If on the upper surface, there may be bulging of the right side of the chest—at first only at the lower part, but later almost universally, with a more open curve to the costal arch, and widening and bulging of the intercostal spaces even beyond the level of the ribs. The thoracic hepatic dulness is increased upwards; in one case it was as high as the first rib. It is often dome-shaped in the front, the side, or the back of the chest. Percussion in the intercostal spaces gives the sensation of great resistance.



The heart may be displaced to the left if the parasite is in the right lobe, or be raised or pushed bodily forwards, with an increased force and area of the palpable impulse, if in the left lobe. If the parasite be large and in the substance of the liver, the size of the organ is manifestly increased, either generally or only as regards one, usually the right, lobe. The liver margin is depressed, even to the pelvis; its outline may be normal, elongated at some part, or with a more or less pedunculated outgrowth. The surface is uniformly smooth, or bulged at one spot, the bulging being either regularly convex or more or less lobulated; or if the hydatid be multiple, the liver may be studded with prominent bosses like cancerous nodules. The enlargement is generally firm, and often elastic. Fluctuation is very rarely elicited, percussion does at times yield the hydatid thrill. Jaundice in the absence of suppuration is very unusual, though it has been noted when membranes have entered and blocked the bile-ducts, or the cyst has pressed upon them in the portal fissure. Ascites is so uncommon as to be a pathological curiosity. Rupture of an uninflamed cyst into the peritoneal cavity has caused a voluminous ascites, which yielded bile-stained serum containing hooklets. Occasionally dilated veins course over the lower chest and upper abdomen.

Hydatid of the liver often suppurates, either immediately after aspiratory puncture, tapping with trochar and cannula, or accidental injury: sometimes this event occurs spontaneously, being due, occasionally at any rate, to rupture of a bile-duct into the cyst. The symptoms induced may be quite insignificant; but more often pyrexia of the remittent type supervenes with general constitutional disturbance, rigors, and wasting; the tumour becomes painful and tender, increases noticeably in size, and the skin over it may grow red and resemble a pointing abscess. Jaundice is frequent. When a cyst is in the dome of the liver it leads to pleurisy with abundant serous infusion, or with plastic exudation only.

Unless dealt with surgically a living or a suppurating hydatid of the liver will extend, and discharge itself in one of several directions as follows:—(1) Into the alimentary tract most commonly—either into the intestine, or if in the left lobe, into the stomach. The tumour may thus become tympanitic from entry of gas. The membranes, white or bile-stained, may be vomited or passed by the bowel; and this evacuation may persist for weeks or months, with eventual complete recovery or death from exhaustion. (2) Into a bronchial tube, after the formation of adhesions between the liver, diaphragm, and lung, generally the right. Skins are expectorated, which are colourless, or in some cases deeply bile-stained. When all are thus removed the cavity contracts and health is restored. On the other hand, the patient often dies from exhaustion, the result of prolonged suppuration with hectic symptoms; or from profuse hæmoptysis, gangrene of the lung, or suffocation due to obstruction of the air-passages by a large piece of membrane or an unruptured daughter cyst. (3) Into the pleural sac, producing pleurisy generally suppurative, or pyo-pneumothorax from associated ulceration into a bronchus or the bowel. (4) Into the peritoneal cavity, setting up an intense and generally fatal

peritonitis. If, however, the hydatid has not suppurated, its bursting may occasion only a mild peritonitis with much ascitic accumulation and the eventual development of a general hydatid infection of the abdominal cavity. (5) Through the abdominal wall. (6) Into the gall-bladder or the biliary passages, inducing biliary colic with or without jaundice. (7) Into the pericardial sac. (8) Into the hepatic veins in the substance of the liver, whence the membranes are carried into the pulmonary arteries and cause sudden death or rapidly fatal syncope.

*Diagnosis.*—Hydatid has to be distinguished—(A) from other diseases of the liver causing enlargement; (B) from extra-hepatic affections.

A 1. Lardaceous disease may be simulated by a parasite so deep in the substance of the liver as to cause no globular swelling on its surface, and big enough to enlarge the organ downwards. An associated enlargement of the spleen, and albuminuria, with a history of long-continued suppuration, would indicate waxy liver. When the amyloid condition is due to syphilis the organ may be nodulated from the contraction of fibroid trabeculae, the result of obsolete gummas, and may thus resemble multiple superficial hydatids. Such syphilitic livers, however, are generally painful and tender, and are often immobile on deep inspiration, owing to adhesions from old perihepatitis. A history of syphilis, the existence of present or the evidence of past manifestations, and an associated albuminuria will assist in the diagnosis.

A 2. Cancer of the liver may cause uniform enlargement, local bulging, or multiple bosses, and so resemble hydatids. Rapid increase of the liver or its prominences, pain, tenderness, and jaundice suggest carcinoma; provided suppuration can be excluded by the absence of pyrexia, rigors, etc. So also do cancerous cachexia and wasting, umbilication of the bosses, a history of previous removal of a malignant growth, or the presence of a suspicious neoplasm, either external or internal, *e.g.* per rectum. On the other hand, the patient may be too young to render cancer probable.

A 3. Tropical abscess can only be confounded with a suppurating hydatid. The infrequency of hydatids in the tropics, and of tropical abscess in temperate zones, and the fact that tropical abscess of the liver is in the vast majority of cases preceded or accompanied by dysentery, will aid in forming a decision; though this is not of much moment, as the treatment of the two complaints is identical.

A 4. Nutmeg liver from cardiac failure. A hydatid may exist in the liver of a patient afflicted with heart disease, but a local bulging cannot be due to simple engorgement. A patient with heart disease who has had a hydatid removed from the right lobe has appeared a year or two later with a greatly enlarged left lobe, pyrexia, local tenderness, and some jaundice. History and physical signs suggested a second parasite now suppurating; but inquiry revealed acute rheumatic pains at the onset of feverishness, and improvement on administration of salicylate of sodium, with subsidence of the hepatic enlargement, dissipated the possibility of a suppurating hydatid.

A 5. Though cirrhosis of the liver may give rise to a general increase in size, it is rarely partial so as to produce a local bulging likely to imitate a hydatid tumour. Further, in cirrhosis there is generally a history of alcoholism and of gastric disturbance, often the aspect of overstimulation, and frequently more or less icterus; while the edge of the liver may be hard, and the surface palpably granular.

A 6. A distended gall-bladder may be indistinguishable from a hydatid springing from the under surface of the liver and projecting downwards from its lower margin. Both tumours may be somewhat movable, elastic, and obscurely fluctuating. The gall-bladder is generally larger below and narrower above, and a hydatid the reverse, but not always. A history of sudden pain followed by gradual enlargement would suggest obstruction of the cystic duct by a gallstone; though such obstruction with patency of the common duct and without jaundice is uncommon. Exploratory puncture in the one case might yield a clear, watery, non-albuminous fluid containing hooklets or membranes, and in the other a mucoid or biliary liquid. But it should be remembered that both a distended gall-bladder and a dead hydatid may contain either colourless serum or bile-stained fluid, or, if they have suppurated, a puriform liquid, and that such puncture is not only unreliable on this account, but for other reasons is less desirable than incision.

A 7. Simple cyst of the liver is seldom large enough to be recognised during life. When palpable, its low tension, in marked contrast with the firm, almost solid feel of a hydatid, has raised the suspicion of its non-parasitic nature. When the organ is nodulated, and concomitant nodulation of both kidneys can be detected, non-parasitic cystic disease should be diagnosed. Though multiple hydatids might exist in all these organs, this would be very unlikely. Usually, though not invariably, simple cysts contain serum, but aspiration is not advisable.

B. *Extra-hepatic Affections.*—B 1. Right pleural effusion generally gives an area of dulness, with its upper limit sloping obliquely downwards and forwards from the spine, whereas in hydatid the upper margin of impaired resonance often descends as it approaches the backbone. This test does not apply when the pleural effusion is loculated as the result of old adhesions, or when the patient has habitually leant forwards during his illness, in which case the upper limit of pleural dulness may be higher in front. In pleural effusion a history may be obtained of acute pain, fever, and recent onset without any preceding dyspnoea. A friction sound does not aid in the diagnosis, as it may be heard in either complaint. Pleural effusion, of course, does not exclude hydatid of the liver, since an inflamed cyst may set up pleurisy; but if the effusion be absorbed, or be evacuated, the dulness due to the parasite will remain. An aspirating needle will then withdraw serum at first, and when used again will yield hydatid fluid; or if introduced deeply it may enter the liver and strike the contents of the parasite, and as the needle is being removed it may withdraw serum from the pleural cavity.

B 2. Hydatid at the base of the right lung is usually indistinguish-

able from a parasite on the convexity of the liver. If, however, it does not involve the extreme base of the lung, the existence of a line of resonance between it and the normal hepatic dulness might render a diagnosis possible. It is more likely to cause lateral displacement of the heart, and less likely to produce descent of the liver margin below the costal arch.

B 3. Subphrenic hydatid cannot be diagnosed from the hepatic : for a cyst of the liver may bulge on its upper surface beneath the diaphragm and give rise to identical signs. It has even been known to perforate the diaphragm through an opening not larger than the thumb, and then to expand into a sac large enough to reach the level of the third rib. A diagnosis is not essential, as the treatment is similar.

B 4. Hydronephrosis. Usually on deep inspiration the fingers can be insinuated above a renal tumour, though sometimes a cyst of the kidney is adherent to the liver and continuous with its lower border. Such a tumour fills the lumbar region more than an hepatic hydatid, and the colon may be detected in front of it. The sac may be lobulated, but a hydatid cyst is also sometimes obscurely lobulated. Should sudden diminution of the tumour occur with coincident increase of the quantity of urine voided, hydronephrosis would be probable ; still, this event might happen from rupture of a hydatid into the renal pelvis : this, however, would probably be followed by evacuation of fragments of membrane by the urethra. Aspiration might reveal urine more or less altered, albuminous fluid, pus, blood, or colloid material, or on the other hand characteristic hydatid structures. Sometimes, however, the liquid from a hydronephrosis is clear and limpid with no albumin or but a trace, and much chloride of sodium, thus closely resembling hydatid fluid.

B 5. A pancreatic cyst is generally more centrally placed, occupying the epigastric and umbilical regions, fluctuates more definitely, and usually in the recumbent but more certainly in the erect posture has an area of stomach resonance between it and the liver. This may be rendered more definite by artificial distension of the stomach. The lower border of the liver can also be felt by careful palpation descending in front of the cyst on deep inspiration. Aspiration (if employed) furnishes a fluid which changes starch into sugar or emulsifies fat instead of possessing the characteristic hydatid elements.

B 6. Splenic cyst. *Vide* hydatid of the spleen, p. 1023.

B 7. An ovarian tumour grows from below upwards, is attached to the uterus, and is usually separated from the liver by an area of resonance ; a hydatid grows from the liver downwards, and very rarely enters the pelvis.

B 8. Ascites can only lead to difficulty in diagnosis when the hydatid of the liver is so immense that it fills the whole abdomen, or when the conditions accompanying ascites prevent the intestines from floating forwards to the abdominal wall. Resonance in the flanks and iliac regions would indicate hydatids, but rupture of an hepatic hydatid will occasion ascites with great abdominal distension. Here the bowels may

be matted together so as to suggest tuberculous peritonitis. Paracentesis abdominis may supply many pints of turbid bile-tinged serum, pointing to an hepatic origin of the affection, and hooklets may be found in the liquid drawn off. Cœliotomy will reveal a great number of collapsed bile-stained cysts which have gravitated into the pelvis.

B 9. Floating kidney is distinguished from a pedunculated hydatid by its shape, its softer consistence, its freer mobility in the abdomen, its recession into the lumbar region behind the margin of the liver, and the absence of a band of tissue uniting it to this organ.

B 10. A chronic abscess in the abdominal wall on the right side will have an obscure outline, will not descend with inspiration, and the tissues over and around it will be thickened and œdematous.

*Treatment.*—The only treatment advisable is evacuation of the hydatid by incision. When the liver is not enlarged upwards, but projects below the costal margins, it should be attacked through the abdominal wall. Should the hepatic dulness be much increased above its normal level in the chest, with little or no descent of its border below the costal margin, it should be operated on through the thoracic wall by resection of a portion of rib. If there be marked elevation of the hepatic dulness in the chest, even though the border of the liver may be depressed four or five inches below the costal arch, the sac should be opened through the chest wall; for in these cases the cyst will be found in the dome of the liver. Unless a large local bulging is palpable on the abdominal portion of the organ, an attempt to evacuate the parasite by cœliotomy will probably fail, for only solid liver substance will be met with, or the lower portion only of the sac will be accessible, and when it is emptied it will retract upwards beneath the ribs, and it will be difficult to attach it to the edges of the abdominal incision.

Bile generally drains from the wound after a few days, if not immediately. Its amount may be surprising, and the discharge may continue for weeks and even months, and exercise a deleterious influence on the general health. It gradually ceases spontaneously, but this may be expedited by packing the abdominal wound with gauze.

**Hydatid of the Lung.**—*Symptoms.*—Prior to rupture. If the cyst be small, no symptoms may be noticed: cough, however, is generally present; it varies in severity, but it is rarely paroxysmal as in pertussis. Hæmoptysis, due to active congestion from irritation, to passive distension from pressure, or to a localised pneumonia, usually occurs sooner or later, either copiously or as mere streaks in the mucous sputum; occasionally it is absent throughout. A feeling of weight or discomfort, or the sensation of a foreign body in the chest, may be experienced, but these are uncommon. Dyspnoea increases with the volume of the cyst, but is sometimes slight even when the tumour is very large: it is rarely paroxysmal, but it may be urgent, and be due to pressure on the pulmonary artery or vein. There is no pyrexia unless suppuration, pneumonia, or pleurisy be excited, and only in these circumstances is there any wasting.



*Physical signs* may be wanting if the cyst is small and deeply seated: but when large there may be local swelling, which may be limited to a small area. In rare instances a rib is eroded from pressure, so that part of the cyst projects through the chest wall, and may then closely resemble an extra-thoracic fluid tumour; but its nature may be recognised by a diminution in size when the patient lies down, and in certain cases by the impulse communicated to it on coughing or straining. In very large cysts the intercostal spaces may be widened and somewhat prominent, and may communicate an elastic semi-fluctuating sensation on palpation and percussion. The area where the cyst comes to the surface is quite dull, and yields a marked sense of resistance. If a layer of lung intervene between the cyst and the chest wall a subtympantic or even a skodaic note may be elicited. The respiratory murmur may be weak or even abolished, and this may also hold good as regards the vocal resonance. The heart may be displaced to the right or to the left, according to the situation of the parasite; or be so pressed forwards as to give a greatly increased area of palpable pulsation. Very rarely distinct pulsation is to be felt in a widened intercostal space over a large hydatid, communicated from the heart, against which it presses. Occasionally œdema of one or both arms ensues from pressure on the intra-thoracic veins. The parasite is comparatively opaque to x-rays, and so may be seen with the screen, and in a skiagram (Fig. 229).

Rupture into a bronchus is shewn by the onset of violent suffocative cough, with expectoration of watery fluid, pieces of hydatid membrane and of blood. This may be scanty, or may be so abundant as to threaten or even to terminate life; generally there is urgent dyspnoea. After rupture, cough, of varying frequency and violence, continues until all the cyst is expelled; exacerbations occur at irregular intervals, with expectoration of copious muco-pus, and many skins, fragments of the original cyst, and perhaps daughter cysts recently ruptured. The sputa may be fetid, and hæmorrhage, which may be profuse or even fatal, may come on at any time, and be accounted for by supposed varices, degenerations, ulcerations, or aneurysms of the pulmonary vessels on the walls of the hydatid cavity. No deterioration of the general health may be apparent, although large quantities of membrane may have been coughed up during many months; on the other hand, pyrexia, wasting and hectic, may supervene and rapidly exhaust the patient. Skins may be expectorated abundantly, and yet a careful examination of the chest will fail to reveal their source, as this may be a cavity deep in the substance of the lung which, contracting on its gradually diminishing contents, gives none of the classical signs of a vomica. Usually, however, the physical signs are those ordinarily found in a pulmonary cavity—for example, in phthisis—and vary as widely in different cases: at one time they may be ill-defined, and then, after a profuse expectoration, well marked.

The sac of an uninflamed hydatid may burst into the pleural cavity and establish a pneumothorax, furnishing all its classical signs with evidence of more or less fluid in the pleural cavity. These gradually disappear



after closure of the aperture of rupture, and later the cyst is coughed out of its sac through the bronchial tubes, and thus first reveals the cause of the pneumothorax. In other cases this is demonstrated at the moment of rupture by a coincident copious expectoration of hydatid fluid, with or without the membranes. More frequently the parasite ruptures, its fluid contents are brought up, and its adventitious sac inflames, followed after a few days by a pyo-pneumothorax. This is due to sloughing of its



FIG. 126. Specimen showing from the back, three pulmonary hydatids, two of these very distinctly seen, are symmetrically situated a little above the middle of the lungs. The third, more obscure, has its shadow blended with that of the heart and pericardium on their left side. All three parasites were successfully removed by incision. (From a photograph by A. H. Fryett, Melbourne.)

wall where it is covered only by visceral pleura, or its rupture by urgent and uncontrollable coughing.

Rarely, if ever, has a cyst been found in the pleural cavity. It is probably impossible to diagnose a parasite so situated from one in the substance of the lung. Nor can its exact site be determined even when one or two ribs have been excised and the hydatid cavity has been laid open. For a pulmonary hydatid in its growth reaches the visceral pleura, which becomes fused with the thin adventitious capsule, and subsequently with the parietal layer; so that when incised no pleural

cavity is opened, but the scalpel passes direct from the parietal pleura into the sac. In fact, many hydatids supposed to be pleural are almost certainly pulmonary hydatids which have become superficial.

Not infrequently two and even three separate parasites of no mean size are located in the same lung; but with careful physical examination it is possible to recognise them by the narrow patches of resonant lung which intervene between the larger areas of hydatid dulness.

*Diagnosis.*—1. Pulmonary Tuberculosis. When unruptured, hydatid disease resembles incipient phthisis in the short dry cough, repeated hæmoptysis, and perhaps in some shortness of breath and abnormal physical signs at one spot in the chest. Its hydatid nature is determined by the following considerations:—The signs are most often not at the apex; when they are, they are exceedingly rarely bilateral. The dulness is sharply defined, with weakened breath sound or respiratory silence, and an absence of moist rales. There is no pyrexia. The general health has undergone no deterioration, and although the symptoms may have existed for some months, the strength has not failed.

When ruptured it may be very difficult to distinguish a hydatid cavity from a phthisical vomica, unless it be situated in the base, as most frequently it is, the rest of the lung being healthy. Phthisical vomicæ, too, are very rare in children. If the disease be bilateral it is probably phthisical, for symmetrical pulmonary hydatids, though not unknown, are uncommon. Diarrhœa or laryngeal disease suggests phthisis; nevertheless the former may occur, as a hectic symptom, in prolonged and profuse suppuration from a pulmonary hydatid. The expectoration even of a microscopic fragment of hydatid membrane is conclusive. The membranes, however, frequently undergo gelatiniform degeneration, and become translucent and very soft, and may easily be overlooked by the physician; on the other hand, the patient may mistake shreds of tough, consistent mucus for pieces of “skins.” Tubercle bacilli in the sputum prove the presence of phthisis, but do not exclude hydatid, for now and then the two affections co-exist.

2. Gangrene of the lung resembles ruptured hydatid in the presence of a cavity and the voiding of fetid sputa; but it generally runs a very acute course, membranes are absent from the expectoration, and usually some antecedent cause suggestive of gangrene is known.

3. Pleural effusion is closely imitated by a hydatid at the base. Pain and pyrexia, or a recent history of them, favour pleural effusion. These symptoms may, however, occur in hydatid, if a pleurisy be induced by its irritation, or if it should become inflamed. Dyspnœa is less marked, as a rule, in hydatid, because of its slow growth, and to the accommodation effected by bulging, etc. The line of dulness may help: in a hydatid it is often semicircular, in pleural effusion it slopes from the spine downwards and forwards. In a loculated empyema the dulness may be dome-shaped, but in this case the pyrexia, pain, acuteness of course, and wasting will decide. Displacement of the heart laterally to an extent disproportionate to the area of dulness on the chest wall

indicating a much larger accumulation of fluid in the thorax than is revealed by the superficial dulness, would suggest a hydatid at the base. The shape of the shadow on the x-ray screen or skiagram would assist.

4. Aortic aneurysm may be simulated by a pulmonary hydatid. An area of dulness in the left lateral chest gave an impulse in its upper part, above and outside the site of the heart's apex-beat, and in its lower part in the posterior axillary line. The large area of dulness, with entire absence of expansile character in the pulsation, and of murmur, with the situation and insignificant degree of the impulse, served to distinguish it from aneurysm. It was successfully incised and drained. Conversely a large aortic aneurysm may resemble a pulsating hydatid.

*Treatment.*—When the hydatid is unruptured a portion of one or two ribs should be excised, the cyst laid open, the membranes removed, and the cavity efficiently drained. When there are bilateral hydatids, after one has been extirpated, sufficient time should be allowed for contraction of its cavity before the parasite on the other side is attacked. If there be two on the same side of the chest and both have been recognised (though this discovery is very difficult), they may be dealt with at one operation, through separate incisions. During an operation after removal of the cyst the surrounding lung should be examined with the finger in the sac. The convexity of an adjacent parasite may be palpable; if an exploratory needle yield hydatid fluid, the intervening septum may be divided and the contents of this second sac removed, and both sacs may be drained through the one incision. Some surgeons have recently closed the wound in the pleura and chest wall at once, and others after keeping in a drainage tube for twenty-four hours. Treatment by aspiration is inadmissible for reasons already detailed. If the hydatid has already ruptured and the cysts are being expectorated with little or no pus, no pyrexia, and no failure in health, it is better to temporise; the patient will, most likely, cough up all the membranes, and a spontaneous cure will be effected. If, however, after rupture, a cavity be recognisable, or there be an abnormal area of dulness in the chest, and there be profuse purulent or fetid expectoration, with fever and constitutional disturbance, the proper course is to incise the chest, remove the membranes, and drain efficiently.

**Hydatid of the Spleen.**—*Symptoms.*—Half of the recorded cases were unsuspected during life, and recognised only after death, which would indicate the frequent absence of symptoms. Weight and pain may be felt, and great discomfort on bending forwards. The parasite may rupture into the left lung, into the bowel, or through the parietes of the body.

*Physical Signs.*—A tumour with the classical characters of a splenic enlargement; smooth if the parasite be solitary; lobulated if multiple; sometimes increasing upwards in the chest, sometimes downwards through the left side of the abdomen even into the pelvis, and affording in some cases a perfect hydatid thrill.

*Diagnosis.*—1. A cyst in the left lobe of the liver is often quite

indistinguishable from a hydatid of the spleen. If the hydatid be in its lower pole and project as a globular mass below the costal margin on inspiration, its splenic origin cannot be affirmed unless the notch can be felt above it, nor if the parasite be in its upper pole and push the rest of the spleen beyond the costal arch, unless the bulge of the hydatid can be felt to be in the spleen above its palpable notch. For diagnosis the notch and the tumour must be demonstrably in the same mass, unless the left edge of the liver can be distinctly isolated from the cyst.

2. *Lardaceous Spleen.*—A circumscribed prominence favours the diagnosis of hydatid. On the other hand, uniform enlargement of the liver, a history of syphilitic disease, or of prolonged suppuration with the co-existence of albuminuria, would contra-indicate its presence.

3. *Enlarged Spleen of Hepatic Cirrhosis.*—Here there are usually definite signs of the primary disease—slight jaundice, piles, melæna, hæmatemesis, or marked gastric derangement. Ascites comes on at a later stage.

4. *Abscess of the Spleen.*—A diagnosis from suppurating hydatid is probably impossible, as the previous existence of the living parasite may easily have been overlooked by a patient.

*Treatment.*—The cyst should be opened and drained. The result is favourable. Death has, however, followed from hæmorrhage consequent upon sloughing of the adventitious capsule.

**Hydatid of the Kidney.**—*Symptoms.*—Weight and distension, if large.

*Physical Signs.*—A tumour in the lumbar region, to which an impulse is readily communicable from the loin; on deep inspiration, the fingers may be insinuated above it, isolating it from the liver and the spleen. It is smooth and uniform, if single; or lobulated, if multiple; more or less movable; with or without a hydatid thrill; separated from the liver by an area of resonance and with colon resonance—if this be present—in front of it.

*Course.*—It may exist for many years without affecting the general health, die, and become obsolescent or rupture into the pelvis of the kidney. The latter is the more common event. Pieces of membrane, daughter cysts, scolices, and, generally, a little blood are then passed by the urethra. This may be the first indication of the presence of the parasite, and if the cyst be small, no tumour may be discoverable in the loin. The passage of membranes may occasion attacks of renal colic so violent as to induce convulsions, or they may pass along the ureter without pain. Recovery not infrequently comes about, it may be after years of such discharges. The hydatid may suppurate and then burst into the renal pelvis and cause pyuria. So, too, it may ulcerate into the alimentary canal at some point, into the peritoneal cavity, or into the lung and discharge into a bronchus—in which case the prognosis is rather unfavourable—or even externally. When large, it may be so destructive as to prove fatal.

*Diagnosis.*—The determination of the renal origin of the cyst is

fairly easy, especially on the left side. If, associated with a tumour in the kidney, there be a discharge by the urethra of hydatid products, the diagnosis is complete. Such discharge, however, without a renal tumour is not sufficient; for a hydatid of the pelvic pouch of the peritoneum is nearly as common, and this may open into the bladder. 1. The greatest difficulty is found in distinguishing between a hydatid and a hydronephrosis. In both a renal cyst is felt, in both it may be smooth, round, painless, movable, elastic, and with a perfect hydatid thrill. If it be lobulated it is more likely to be a hydronephrosis; but multiple hydatids or even a solitary one may be lobulated. If a hydatid tumour elsewhere should co-exist, the probability of a renal parasite is much greater. If, however, there be a history of urinary trouble, such as the passing of calculi or of large quantities of urine with a corresponding subsidence of the tumour, a hydronephrosis would be the more likely. In these cases even the aspirator needle will not always decide. Of course if scolices or shreds of membrane be withdrawn, an absolute diagnosis is possible, but not otherwise; for though the aspiration of urine would favour hydronephrosis, yet this is said to pass by osmosis into hydatids, to the extent of forming deposits of triple phosphate crystals in the interior of daughter cysts, or even calculi as large as peas. Though clear limpid fluid, exactly resembling that of a hydatid, be evacuated, giving no albumin, or only a trace, and abundance of sodium chloride, it may, as likely as not, be a hydronephrosis, which not infrequently has similar contents. Even a trace of urea does not negative hydatid fluid, of which, in minute quantities, it is a normal constituent. The presence of albumin in large quantity, though common in hydronephrosis, may be found in a hydatid which has recently died. Sometimes, therefore, the distinction between the two renal affections is an impossibility. Fortunately the treatment demanded is the same for both, namely, free incision and drainage.

2. Cystic disease of the kidney, congenital or acquired, may closely resemble multiple renal hydatids. Implication of both kidneys would suggest the former; and a palpable cyst in the liver with one kidney also involved, the latter.

3. *Ovarian and Parovarian Cysts*.—These grow from below upwards, and are generally known by their proper signs on combined vaginal and abdominal examination.

When suppurating, a hydatid cyst must be distinguished from pyelitis, simple or calculous; pyonephrosis; renal tuberculosis; and abscess, renal or perinephric. The special products of the hydatid, tubercle bacilli, or fragments of calculus discovered in the urine, are probably the only distinctions.

*Treatment*.—If cysts or shreds are passing by the urethra without much pain, and there is no deterioration of general health, the cure may be left to nature; if a renal tumour exist or there be much distress or suppuration with reduction of strength and weight, an operation should be undertaken.

**Hydatid of the Omentum, Mesentery, and Peritoneum.** *Hydatid signs.* One or more tumours are visible or palpable, generally very movable, both by the hands of the examiner and on change of position, they appear also to be unconnected directly with any of the abdominal viscera. They frequently acquire a very thick hard capsule, even when of small size, so as to feel like solid growths.

*Diagnosis.* — Floating kidney. A hydatid is seldom quite of the same shape as a kidney, it is often too movable; the kidney may be palpable on inspiration, at the same time as the tumour.

Diagnosis from omental sarcomas in the young, and even from uterine myomas, ovarian cystomas, and malignant disease in the pelvis, when they are multiple, is often impossible without puncture; and their nature is frequently determined only during an exploratory laparotomy.

*Treatment.* They should be operated upon. Sometimes they can be removed entire in their sac by separation of adhesions or tying off the piece of omentum in which they lie; this is the ideal method; sometimes by Bond's operation, or by drainage. When low in the pelvis it may be safer and more convenient to operate through the perineum, or the vagina.

**Intracranial Hydatid.** *Symptoms.* — An intracranial hydatid, is essentially an innocent, slowly growing tumour, and gives rise to the usual symptoms of such a neoplasm. It may occupy any position, being extra cerebral between the skull and the brain, or intra-cerebral in the cerebrum or cerebellum, or intra-ventricular. It may be in the frontal, parietal, or occipital lobe, extra-cortical, cortical, subcortical or wholly in the white substance. It may attain very large dimensions, so as to hold more than a pint of fluid. There may be a solitary cyst, with or without contained daughter cysts, or more than one cyst in a single cavity without a mother cyst, the several cysts being free from one another or externally attached as though from exogenous multiplication, or two cavities may be present with one or more cysts in each and with one, two, or three cysts in the lateral ventricle. These cavities may communicate with one another. There may be no adventitious membrane lining them, or only a microscopic one. A hydatid may, therefore, afford very marked, only indefinite, or no localising symptoms, either subjective or objective, just like any other benign tumour in the same situation, and any symptoms ordinarily induced by a benign tumour of the brain may be met with. Nothing in the character of the individual manifestations or their grouping indicates the hydatid nature of the disease.

*Diagnosis* involves three points, viz. the presence of a tumour in situation, and its nature. The first two must be decided on general principles of diagnosis. Then an opinion as to its being a hydatid will rest upon the following considerations — 1. There should be no positive indications of other disease such as syphilis, affections of the ear, nose, or skull, tuberculosis of the lungs, no history or evidence of malignant disease elsewhere. 2. In a country or district where hydatids are prevalent the possibility should not be forgotten. 3. It may cause a uniform enlarge-



ment of the cranium, a local bulging, a localised thinning so as to yield egg shell crackling, or even a perforation. 4. The mean age of patients with tuberculous tumour is twelve and a half years, that of echinococcus is twenty-two years; therefore a tumour of the brain in a child is more likely to be tuberculous than hydatid, in a young adult the reverse may be expected. Cerebral hydatids are fourteen times as common as cerebellar, therefore a cerebellar tumour is probably not a hydatid. Since tuberculous tumours are as common in the cerebellum as in the cerebrum, a cerebellar tumour in a child is much more likely to be tuberculous than hydatid. 5. A hydatid elsewhere in the patient would strongly support the diagnosis of a cerebral hydatid. 6. It has been proposed to pierce the skull with an instrument like a watchmaker's drill, and explore with a large hypodermic needle. But localisation is often not sufficiently exact to make this plan of much service. Membrane or booklets might be withdrawn, but without these it would be difficult to distinguish cerebrospinal from hydatid fluid.

*Prognosis.* Most patients die, suddenly during an epileptiform fit or while vomiting, more or less rapidly from increasing stupor and coma, and progressive paralysis and asthenia, or from some intercurrent disease. The duration of life will vary with the site and rapidity of the growth. Life has been prolonged for five years after the first symptoms were noted. Some cases have recovered after spontaneous perforation of the skull and evacuation of cysts, which was either spontaneous or followed simple incision of the scalp; but such cases are very rare, and were probably extra-cerebral.

*Treatment.*—When an intracranial hydatid is diagnosed or strongly suspected, one course only is open, viz. to trephine the cranium and remove the parasite. This may be done at one operation, but some surgeons divide it into two stages with an interval of three or four days; at the first stage the cyst is tapped and its fluid withdrawn, at the second it is removed. Several successful cases have been recorded in which recovery has been complete and permanent; but motor and sensory paralysis, in greater or less degree, may remain, and in some instances as late as twelve months after apparently perfect recovery a fatal relapse has taken place and autopsy has revealed several other hydatids. Special complications and dangers surround operations for removal of hydatids from the brain, and render interference less satisfactory than in the case of the other viscera; for instance, after an easy and complete evacuation of the parasite the patient may die in a few hours, from hyperpyrexia and epileptiform convulsions.

**Hydatid of the spinal cord** is rare. The parasite may be wholly within the spinal canal, or partly inside and partly outside. It invades the canal from the tissues and cavities adjacent and from the vertebrae. Or it originates within the canal, and thence extends by absorption of bone through the intervertebral foramina and between the spinal laminae into the muscular tissues of the back or into the thorax and abdomen in front. There seems to be a special tendency to burrow,

a feature of hydatids which is discussed elsewhere,—thus one or more cysts may be found within the canal, others in the muscular planes of the back, and others within the thorax, but all contained in one sinuous lobulated cavity. From the spinal canal outside the dura mater they may penetrate this membrane, and lead to the disorganisation of the cord. The bones of the vertebral column in some cases are infiltrated with an immense number of minute cysts which fill the small spaces of the cancellous tissue, not only in the bodies but also in the transverse and articular processes and the arches. They may hollow out cavities in the bone which will be packed with tiny cysts. They are, however, the ordinary *Echinococcus hydatidosus*; for when they get into the spinal canal, the chest, or the abdomen they become of the usual size, their small dimensions, when confined within the bone, being apparently only due to their environment.

*Symptoms.*—The symptoms are such as would be caused by an innocent tumour within the spinal canal; namely, radiating pains from pressure on the spinal nerve-roots, and the motor and sensory phenomena of compression of the spinal cord, with or without those of a supervening compression-myelitis. Sometimes the indications are those of a chronic myelitis only. When such symptoms are present a suspicion of their hydatid origin may be entertained if a cyst is detected in some other part of the body, but certainty can only be obtained if part of the parasite projects externally in the back, and on aspiration yields hydatid structures or fluid.

*Treatment.*—If detected or strongly suspected, removal by incision should be attempted. Hitherto the results have been very unfavourable. Two special circumstances lead to failure. The canal is opened, and cysts are found and removed, but no improvement follows, and the patient eventually dies, when autopsy reveals one or more cysts further down the cord. Again, at the operation, the spinal bones are discovered to be stuffed with tiny hydatids, for which no rational plan of cure has yet suggested itself.

**Hydatid of the heart** is so rarely found that it is a pathological curiosity. It has never been diagnosed during life, and is not known to give rise to any symptoms. The following are the notes of a case. A girl had been passed as eligible for life assurance. Three weeks afterwards she left the kitchen to bring in some firewood, and was found a few minutes afterwards on the woodheap, unconscious, with some twitching of her arms and legs, and died in about ten minutes. The posterior wall of the left auricle was occupied by a hydatid cyst as large as an orange, which had ruptured into the auricle. The heart with the empty cyst weighed thirteen ounces. The left carotid was blocked by a daughter cyst at its point of entrance into the cranium.

**Extravisceral Hydatids.**—Though these have frequently been alluded to as illustrating modes of growth and pathological features, their treatment usually falls within the province of the surgeon rather than of the physician. The same general principles of treatment.

however, as have been indicated, are applicable here also. But when a long bone becomes the nidus of the parasite, amputation of the affected member will almost certainly become, even if it be not so in the first place, the necessary treatment. In hydatids of bone where amputation is impracticable, it is to be noticed that local injections of potassium permanganate have proved beneficial, and in such cases this principle of treatment requires further trial.

#### ECHINOCOCCUS ALVEOLARIS SIVE MULTILOCULARIS

For reasons previously stated we prefer to distinguish this form of hydatid under the first of these names. Occurring both in man and some animals, with by far the greatest frequency in the liver, where it may attain any size up to that of an adult's head, it nearly always leads to a fatal result. In its broad structural features the main mass of such a tumour consists of a vacuolated or sponge-like stroma of sclerosed connective-tissue, more or less infiltrated with lime salts. This disposition of its framework defines numerous alveolar cavities, varying in diameter from 1-5 mm., which are filled with plugs of colloid material, consisting of plicated and crumpled chitinous vesicles having the same laminated structure and chemical composition as those of ordinary hydatidose cysts. Both surfaces of the individual folds of the vesicles are coated with a finely granular layer of protoplasm associated with other parasitic elements, such as fully formed scolices or detached hooklets. Such a primary tumour may give rise to neighbouring and satellite growths in the same viscus, or to metastases in distant organs. Before it attains any considerable size, which only happens in the liver, retrogressive and necrotic changes, aided by septic infection and bile irruption, produce, towards the centre of the growth, a ragged and anfractuous cavity, filled with bile-stained, sero-purulent fluid, holding in suspension calcareous particles, cholesterin, bilirubin, and other detritus.

**History.**—Noticed first by Ruysch in 1721, a tumour of this character was described in 1852 by Buhl as "alveolar colloid" and later in the same year by Luschka as "colloid cancer" on the strength of its malignant course and histological characters. In 1854 Zeller found hooklets in a similar growth, but considered them to be of accidental origin. Two years later, in 1856, its helminthic origin was recognised by Virchow, who gave it the name of "ulcerative multilocular echinococcus tumour"; and thirty-seven years later, in 1883, the same authority reiterated his belief in the identity of the parent worm of this parasite with that known to be responsible for the hydatidose or cystic variety, attributing the structural differences of the alveolar echinococcus to differences in the histological build of the part infected. Thus he considered that the wandering embryo producing this form came to rest in a lymphatic vessel of the liver, and later he stated that bone also must be considered as a nidus determining the assumption of the alveolar type. Virchow inclined to the view that it multiplied and

extended by a local production of exogenous buds rather than to the view held by some other writers that each constituent vesicle of the whole growth was the product of a separate and independent embryo; in other words, that the tumour resulted from the coming to rest in a circumscribed area of an embolic shower of such embryos. The latter view is of some interest, for it indicated the unsuspected fact that embryos, rather than scolices, were the objects to be sought for, and thus in a sense it, in part, anticipates Melnikow Raswedenkow's views, which must be discussed at some length. Virchow, as we have seen, held that the settlement of the embryo in a lymphatic was one of the factors in determining the alveolar character of this kind of hydatid. Leuckart and Erismann ascribed a similar rôle to the blood-vessels, Friederich to the bile-ducts, and Liebermeister to all three kinds of vessels.

Virchow's great authority held sway for half a century, yet of recent years, doubts have arisen as to the specific unity of the parasites causing the hydatidose and the alveolar forms of the disease. Those, however, who have asserted a duality of species have not done so on the same grounds. V. Mangold and Müller, as the results of feeding experiments, maintained that they had produced a different tænia, principally because in the ripe terminal segment the ova were aggregated in a spherical mass instead of being distributed in branched clusters as is usual in the tænia of von Siebold. The single "clumped" arrangement may, however, undoubtedly occur in the true *T. echinococcus* (see Figs. 215 and 216). Posselt and others, as the result of micrometric measurements, believed that the shape and size of the hooks of the scolices in *E. alveolaris* differed from those of the common form, in being longer, thinner, and less curved; but there is equally no doubt that many and similar variations may occur in the hooklets of *T. echinococcus*. The Russian authority Melnikow Raswedenkow, after a very exhaustive study of the subject, bases his advocacy of a duality of species on various grounds, such as its peculiar mode of growth and reproduction, its reaction to the containing tissues, and its somewhat restricted geographical distribution. In confuting Virchow's dictum, that the two forms are determined by differences of the tissue conditions of the affected part, Melnikow-Raswedenkow insists that both the cystic and alveolar forms may be found not only in the same animal but in the same viscus. This writer considers that the parasite of the alveolar echinococcus occupies an intermediate position between the Cestodes (tapeworms) and the Trematodes (flukes), from its power of producing amoeboid embryos *in loco*; this point, however, will be dealt with in the next section.

On the whole, it seems impossible to resist the conclusion that we have, in this alveolar form, to deal with a parasite specifically distinct from that of the common hydatid.

**Pathology.**—In this respect, as in its biological aspects, very little has been added to our knowledge since the observations of Virchow and the other early investigators, and, indeed, it is not a little remark-

able from any point of view that a disease so formidable, so fatal, and so peculiar in many respects should have received such scant notice in text-books. There is, in fact, no doubt that from the restricted area of its distribution the majority of writers have never come in contact with it; while those only who have had opportunity of noting its fatal effects realise its importance. Of recent years, however, alveolar echinococcus has received increased attention from various Russian and German writers, and notably from Melnikow-Raswedenkow, who has embodied the results of an extensive study of this disease in his monograph published in 1901. To his views, which appear to throw new light on this remarkable parasite, we must now devote some attention. He points out a fundamental structural difference between the bladders of the hydatidose echinococcus and the chitinous vesicles of the alveolar form, inasmuch as in the former the embryonic parenchymatous layer from which scolices are developed is limited to the inside of the chitinous cyst, while in the latter this reproductive material is disposed not only within but on the outside as well. With this internal disposition, in the one case, he correlates the tolerant reaction of the host's tissues to the parasite, which are limited to the changes induced by the mechanical pressure of the growing parasite. We have, indeed, already spoken of these relations as being essentially symbiotic in their character. With this tolerance he contrasts the violent reaction of the tissues induced by the presence of the parasite of the alveolar hydatid, in consequence of the presence of the active reproductive substance, which is in direct contact with the tissue-elements, instead of being separated from these, as in the hydatidose echinococci, by the thick chitinous membrane. And, moreover, this living embryonic substance is capable of producing, not only scolices, but also living amœboid embryos after the manner of an animal, and toxins like certain pathogenetic vegetable organisms. It is by means of these embryos, which are endowed with the power of amœboid movement, that extension of the growth by continuity takes place, or, if the embryos should gain entrance into a blood-vessel, metastases in distant viscera may be produced. In any case the secondary tumours may, by the resumption of the parental activities, start new centres of violent toxic reaction in the containing tissues. This process is the fundamental feature of the view advanced by Melnikow-Raswedenkow, but it will now be advisable to follow his account of the mode of formation and structure of the alveolar echinococcus tumours.

An embryo of this parasite, which, as we have said, he considers specifically distinct, having wandered into a portal radicle, comes eventually to rest, but instead of becoming a voluminous spherical fluid-containing bladder, as in the hydatidose form of echinococcus, it develops into a distorted and much-folded chitinous vesicle (*Chitinknäuel*), which contains, both between its folds and between these and the wall of the containing cavity, the finely granular protoplasm which serves the purposes of reproduction, and is the source of its poisonous activities.



The toxins of the parasite in its intravascular nidus set up endophlebitis, and subsequent necrosis of the intima, and, by means of outgrowing off-sets, or outrunning processes, from the chitinous structure, which perforate the vessel-wall and penetrate the tissue-elements, the parasite forms for itself an alveolus in Glisson's capsule. Or similar cavities may be formed in the tissue-spaces independently of the blood-vessels. The contorted chitinous vesicle is the homologue, not of an ordinary echinococcus bladder but of a ripe segment of a tænia, because, like the latter, it can produce living embryos; these, again, are capable of repeating the activities of its parent either in adjacent tissues or distant organs. Hence its malignant characters and at the same time the explanation of its multilocular character. The active factor in the reproductive process is the finely granular protoplasm which lies outside as well as inside the folds of the chitinous formation, and may manifest its activities under three forms—(1) scolices, as in ordinary hydatids; (2) immature embryos, more or less spherical and without a capsule (Jugendform); and (3) mature ovoid embryos with a chitinous capsule.

The scolices, being developed in embryonic tissue which, contrary to what happens in the *E. hydatidosus*, is directly in contact with the tissues of the host, are consequently exposed to the phagocytic action of the tissue-cells, and so become destroyed. It is for this reason that scolices are difficult to find in the tumour formation of *Echinococcus alveolaris*. The same reason, according to this writer, accounts for the almost constant failure of feeding experiments, except those of v. Mangold and Müller; for, apart from their paucity in number, the scolices reach the intestines of the dog in an exhausted condition. On the other hand, feeding experiments with the endogenously produced scolices of *Echinococcus hydatidosus* are generally successful, because these are in full vigour consequent on their development within a cavity which protects them from the phagocytic action of the host's tissues.

The immature embryos (Jugendform) wander into the lymphatics and blood-capillaries, and there develop into sterile and abortive vesicles, which eventually disappear in the necrotic changes wrought by their own toxins amongst the tissue-elements of the part.

A like fate may befall some of the ovoid embryos; others of these, if their vigour be reduced or if the tissue-reaction be strong enough, may become encapsulated by firm connective-tissue, and in these circumstances the parasite dies and undergoes calcareous infiltration: more often, however, they also fall victims to the necrotic processes which they initiate. Other ovoid embryos, again, may make their way into blood or lymphatic vessels by amoeboid movements, and be carried like emboli to distant organs where they form metastases.

The presence of a surviving parasite leads, on the one hand, to sclerosis of the connective-tissue of the part, and thus to an alveolar formation, and, on the other hand, to caseous degeneration which may affect both the neoplasm and the adjacent parenchyma of the viscus.



According to the predominance of the one or the other of these changes, Melnikow-Raswedenkow classifies these tumours as belonging to ( $\alpha$ ) an alveolar, ( $\beta$ ) a caseous, or ( $\gamma$ ) to a mixed form in which both kinds of changes may co-exist to an equal degree. The alveolar form prevails in primary tumours, and the caseous in secondary or metastatic growths.

**Morbid Anatomy.**—In the light of its mode of origin we may now consider a little more in detail the general structure of the tumour of an alveolar echinococcus. The stroma defining the characteristic alveolar spaces consists principally of a firm sclerosed connective-tissue derived from the organ in which the growth has developed; between the constituent fibrillæ of this is a finely granular detritus, consisting of remnants of degenerated cells of the organ, the protoplasmic substance of the parasite and abortive vesicles resulting from arrested development of some of the embryos formed therefrom. With the continued growth of the parasite disturbances of nutrition supervene, due partly to mechanical pressure, and partly to the toxic influences exerted by the embryos, especially by the immature forms. As an additional factor there is obliterating endarteritis in the immediate vicinity of the tumour which accounts for the absence of bleeding on section that has frequently been observed. The alveoli contain more or less numerous plugs of colloid material which are easily removed with forceps, and are, in effect, greatly contorted and folded chitinous vesicles with the embryonic protoplasmic substance disposed as previously described. These vesicles, being endowed with the faculty of producing living embryos, are the homologues of the terminal segments of the tænia in the intestinal canal of the intermediate host. The alveoli are, for the most part, aggregated towards the centre, but they may be scattered throughout the whole growth; they are, independently of the contained vesicles, lined by a thin chitinous layer. Eventually caseation, preceded by coagulation-necrosis of toxic origin, ensues and produces a condition resembling that of a gumma or solitary tubercle. The caseous foci are permeated by a felt-like disposition of fine fibres. Thus the tumour, at this stage, represents an extinguished inflammatory centre in which degeneration and necrosis have predominated.

The peripheral or boundary layer of the tumour, the outline of which is uneven, is composed of granulation-tissue, and presents a cavernous structure, the spaces, however, being microscopic and not macroscopic as in the case of the alveoli. This zone contains numerous immature forms which may emigrate farther into the neighbouring tissues, which shew endarteritis and endophlebitis, and characteristic granulomas enclosing embryos and containing epithelioid, lymphoid, and giant-cells. Sooner or later in almost all primary tumours the centre of the growth breaks down, thus leading to the formation of an anfractuous, and often large, cavity which is the outcome of destructive changes wrought by irruption of bile and by pyogenetic infection. The cavity has ragged walls, and is filled with purulent, bile-stained fluid containing shreds of chitin, fragments of the organ involved, scolices, hooklets, bilirubin, cholesterin, fat-

crystals, and chalky concretions. Thus the fluid of these tumours is a pathological product, and not physiological as in the case of hydatidose echinococci. Such cavities are very similar in character to those resulting from tuberculous excavation of the lungs. In metastatic tumours, which do not assume large dimensions though they undergo caseous degeneration, excavation is generally absent.

As with ordinary echinococcus tumours, so also with the alveolar form ; when a part of a viscus is occupied by a parasite the remainder undergoes a compensatory hypertrophy, a condition which, when it occurs, should be significant to the exploring surgeon.

Primary alveolar echinococcus tumour occurs in man with by far the greatest frequency in the liver ; in other organs it is rare, but primary growths, although not broken down in the centre as in the liver tumours, have been found in the brain, spleen, lung, kidney, and adrenals (Melnikow-Raswedenkow). On the other hand, metastases from a liver tumour occur most frequently in the lungs, lymphatic glands, and brain.

**Geographical Distribution.**—Utilising Posselt’s statistics, and adding 20 additional cases of his own, Melnikow-Raswedenkow records a total of 235 collected from all sources. The analysis of these 235 cases shews a remarkable geographical distribution, for no less than 214 of them can be assigned to the following regions :—

Bavaria . . . . .	57
Tyrol and other Austrian Alpine districts . . . . .	30
Switzerland . . . . .	32
Württemberg . . . . .	25
Russia, including East Siberia . . . . .	70
	<hr/>
	214

The remainder for the most part occurred as single cases or in numbers not exceeding two or three in various other South German or Central European districts, while three are recorded from Italy, one (or two) from France, and one (a German) from the United States.<sup>1</sup> None have occurred in Great Britain or in Iceland and Australia, where *Echinococcus hydatidosus* is so common. South Germany, Switzerland, and the Austrian Alpine region, on the one hand, and Russia (including East Siberia), of which the Moscow and Kasan districts seem to be the chief centres, on the other, stand out as the two principal regions where the alveolar echinococcus is endemic and relatively prevalent. In seeking to correlate the prevalence of this disease within such comparatively restricted areas with its causes Posselt emphasises the fact that of the domestic animals great cattle are almost exclusively affected with it, while it is exceedingly rare amongst sheep and swine ; and he further states that the areas of distribution of the disease for man and cattle coincide. With this he contrasts the prevalence of hydatidose echinococci, to the complete exclusion of the alveolar form, in such countries as

<sup>1</sup> Professor Osler refers to six cases in the United States, chiefly in Germans.

Iceland and Australia, and in such European districts as Mecklenburg, Pomerania, and Dalmatia, where the sheep industry is dominant over that of cattle. From such considerations human infection is, according to this writer, attributable to the association of man with the beasts in question, often in close confinement in stables and under conditions which are filthy in the extreme. Though he is unable to state the exact means by which man is infected, he implies that the dog is an unnecessary factor in the process, and, as already stated, he adopts the view that the alveolar echinococcus is the product of a *tænia* specifically different from that giving rise to the hydatidose variety. Against this view of the agency of cattle Melnikow-Raswedenkow raises the pertinent objection that in the majority of the Russian cases (of which he himself brings forward so large a number in addition to those of Posselt as to constitute Russia the principal centre) infection cannot be thus explained, inasmuch as the greater number of the sufferers followed occupations which did not bring them into special association with cattle. Moreover, he points out that in Russia there is no line of demarcation between the areas of distribution of the alveolar and hydatidose forms. Nevertheless, it remains true that, generally speaking, there exists a remarkable difference in the areas of distribution of the two forms of parasite; this in itself is very significant.

**Occurrence in Animals.**—In contradistinction to the *Echinococcus hydatidosus*, which has been found in a considerable number of different animals, the alveolar form is, as yet, only known to occur in large cattle, sheep, and pigs—in the first-named with considerable frequency, in the last two but rarely. Its biological features, general characters, pathological conditions and effects upon the tissues of the host are in the main the same as in man, but it is stated that excavation is less frequent and scolices more rarely present than in man.

**Clinical Aspects.**—As a primary tumour it has been found in the liver, the brain, the spleen, lung, the kidney, and adrenals, and as secondary or metastatic deposits in the lymphatic glands, lungs, diaphragm, gall-bladder, peritoneum, mesentery, and kidneys. It has generally been unexpectedly discovered post-mortem, having been quite overlooked during life. But of later years it has been diagnosed in several instances when affecting the liver.

**The Liver.**—*Alveolar echinococcus symptoms.*—The earliest manifestations are usually gastric and intestinal disturbances, such as anorexia, nausea, vomiting, constipation or diarrhoea, with perhaps weight and fulness in the hepatic region, but in many cases appetite and digestion have been perfect. Jaundice is specially frequent, occurring in 80 per cent of the cases according to recent statistics. It comes on early, on an average about two years before death, and is sometimes the first symptom; it is well marked and often intense, is persistent and fairly constant in degree, though it occasionally remits, especially if the growth should soften and diminish. It gradually induces its usual concomitants, pale stools, choluria, slow pulse, pruritus, hæmorrhages, emaciation, and weak-

ness, and is most commonly the cause of death. Patients in whom icterus is absent or slight generally live longer. From pressure on the portal vein or invasion of its walls ascites and enlargement of the spleen may result, but both these conditions are uncommon. Interference with the return of blood through the inferior vena cava occasionally produces oedema of the legs, and dilatation of the veins in the abdominal wall. Pyrexia, when present, is due either to complications or to inflammation in or around the liver. If the parasite be central the liver is uniformly enlarged upwards or downwards, with perhaps a rounded edge, and a firm consistence, so as to simulate a large cirrhotic liver. But if situated on or near its surface a nodulated, very hard outgrowth results. Sometimes even then its inequalities are counterbalanced by great thickening of the capsule between them so as to yield a dense uniform, almost stony prominence. Should its centre undergo degenerative softening the tumour will be soft or even fluctuating to palpation. Tenderness is absent unless localised peritonitis or perihepatitis supervenes.

The duration of life varies, and generally extends to several years; in one case it was fifteen after invasion by the parasite.

*Diagnosis.*—From cirrhosis of the liver. (a) In the early stage of enlargement the liver is uniformly increased in size, slightly tender, smooth, and not very hard. There is a history or the evidence of alcoholism, and dyspeptic symptoms are marked, and there may be evidence that the patient has never lived in a locality where the *Echinococcus alveolaris* is endemic. (b) In the contracted stage the organ is small, with a granulated surface, and uniformly firm. Jaundice is late and only moderate, ascites is marked, splenic enlargement considerable, and the general health much impaired.

In carcinoma, which resembles alveolar hydatid more closely than does any other disease, the liver may be very greatly enlarged and very tender on pressure, with marked alteration in form, a very irregular margin, and with bosses perhaps umbilicated, not of stony hardness, nor with any extensive area of softness or fluctuation. It nearly always occurs in later life, is of short duration, rarely lasting more than a year, and is associated with much wasting and cachexia, and with ascites. The spleen is not enlarged, and it may be clear that the patient does not come from an infected district.

From *Echinococcus hydatulosus*.—This may occur in childhood (the *E. alveolaris* has not been observed before puberty). The prominence may be a large, round, smooth elastic cyst, not stony and not fluctuating. Icterus is scarcely ever present apart from suppuration. It is found commonly in certain districts, as Iceland, Australia, etc., where *E. alveolaris* is unknown; whereas this is endemic in other parts as Russia, Bavaria, Switzerland, and the Tyrol.

As aids to diagnosis the sputum, urine, and feces should be examined for ovoid embryos or other constituents discharged from metastases in the lungs, the kidneys, and the bowels.

In a case of primary alveolar hydatid of the lung recorded by Renou

a pneumothorax, which had existed for two years, became transformed into a pyo-pneumothorax shortly before death. The existence of the parasite was not suspected during life.

*Treatment.*—This has so far been very unsatisfactory. It has, in two or three instances, been shewn that a primary tumour of the liver can be removed with a successful result, provided it be discovered sufficiently early, but this, from the difficulty of diagnosis in an early stage, has very rarely happened. On the other hand, all surgical interference with large tumours, especially when excavation has taken place, has been totally unsuccessful, or even impracticable, from the difficulty of removing the whole focus of infection; some attempts, indeed, have been attended with disastrous results from profuse and fatal hæmorrhage. The first consideration, therefore, from a therapeutic point of view, is to improve the method of diagnosis so that tumours may be discovered at a stage sufficiently early to permit of their removal. Partial removal or evacuation of the fluid contents are, of course, futile, as the active part of the growth, with potentialities for further spread and dissemination, is left.

Attempts have been made to destroy the activities of the growth by the local use of parasiticial fluids, and in one such case the repeated injection of formalin, through a surgically established fistula, was distinctly beneficial as regards the general conditions, though the patient died eventually from intercurrent tuberculosis. Such a case, however, encourages the continued trial of all substances likely to have a local parasiticial effect. In the meanwhile, efforts should be made to obtain some substance, possibly a prophylactic or curative serum, which might act through the blood; in this relation the beneficial effect of iodide of potassium on the analogous infective granulomas of syphilis and actinomycosis suggests that this drug should be thoroughly tried in the case of this parasite. Seeing that the active agents in alveolar echinococcus disease are the amœboid embryos, the problem to be solved here is of the same nature as in amœbic abscess of the liver and in trypanosomiasis, in which the parasites to be destroyed are of a protozoan nature. In amœbic abscess the analogy with echinococcus disease is close, for in both there is a suppurating cavity with the actively destructive embryos congregated at the periphery of the tumour. But though, both for the parasites of hepatic abscess and of trypanosomiasis, several substances have been shewn to be lethal outside the body, none, with the possible exception of injection of quinine in amœbic abscess (Rogers and Wilson), have yet been effectual *intra vitam*. Nevertheless the investigations in these diseases indicate the lines on which we must proceed in alveolar echinococcus for the discovery of a cure by medical treatment. As Melnikow-Raswedenkow remarks, the treatment of infectious diseases has been successful just in proportion as we have attained to a knowledge of the life-history and conditions of the causative agent; thus here, also, more complete information on this head is the first requisite for progress in therapeutics.

In the absence of an adequate knowledge of the biological aspect of



the subject we are unable to speak of means of prophylaxis, for we do not know the source from which infection is in the first place derived. There is no direct evidence to implicate the dog as an intermediate host, as in ordinary hydatids, and though, as stated above, Posselt believes the human disease to be in some way associated with its occurrence in horned cattle, yet, from what has appeared under the head of geographical distribution, this view cannot be said to be established. It is, however, satisfactory that, after a long period during which our knowledge of this malignant and dangerous malady has remained stationary, it has of recent years received increased and intelligent study at the hands of some very competent investigators from whose work much new and important information has already accrued.

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### **Echinococcus alveolaris**

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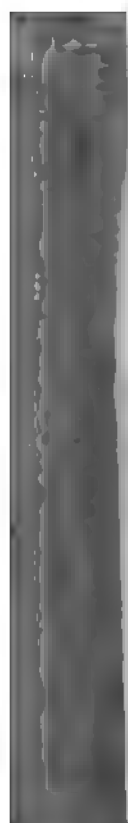
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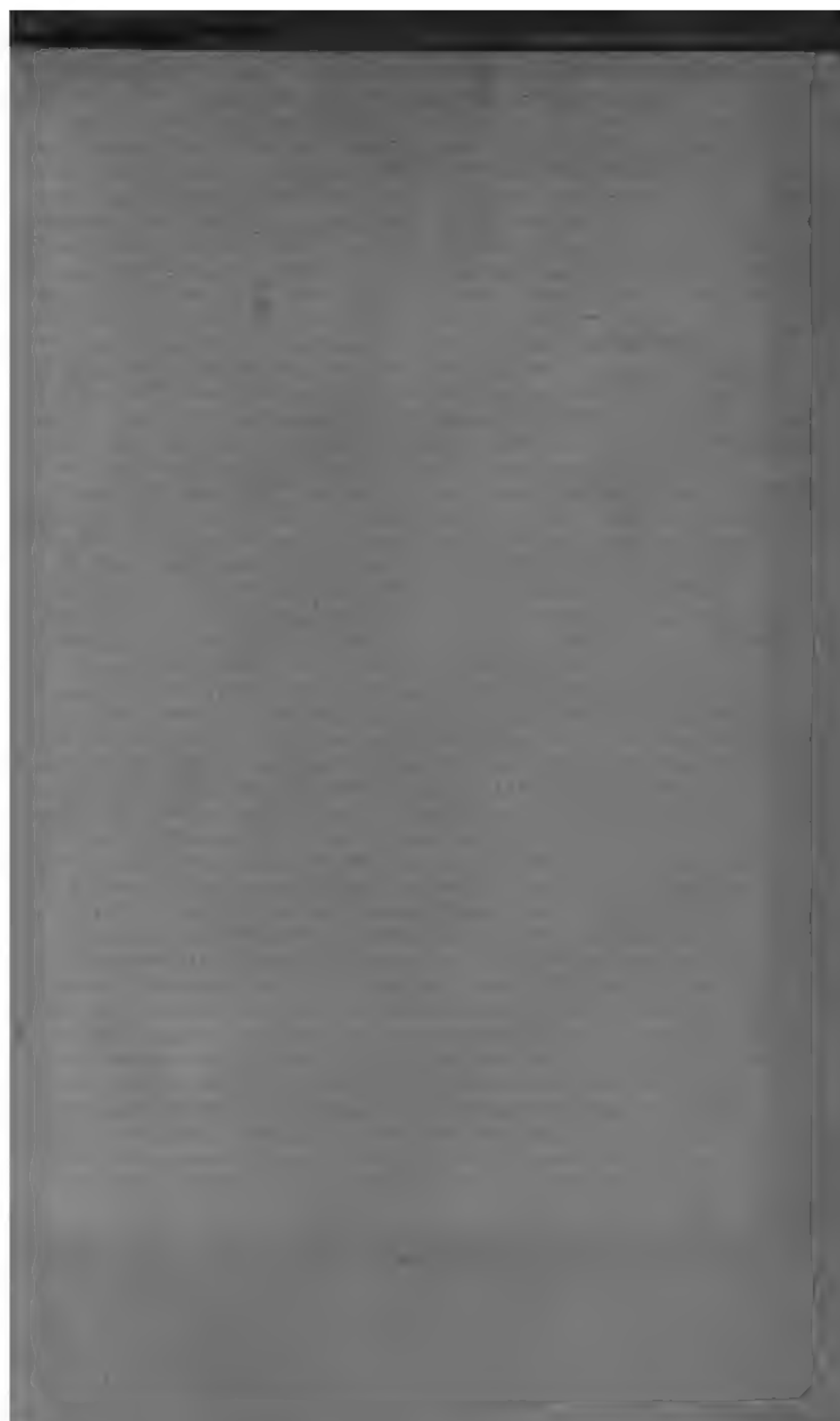
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